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Vol. 211, No. 2 — FEBRUARY, 1946 — No. 887

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

REG. U. S. PAT. OFF.

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

FEBRUARY, 1946

ORIGINAL ARTICLES

MENINGOCOCCUS MYOCARDITIS

REPORT OF TWO CASES WITH ANATOMICAL AND CLINICAL CHARACTERISTICS

BY LT. COL. DELAVAN V. HOLMAN, M.C., A.U.S.,
180TH GENERAL HOSPITAL, APO 513, NEW YORK
AND
LT. COL. D. MURRAY ANGEVINE, M.C., A.U.S.*
FIRST MEDICAL GENERAL LABORATORY, APO 519 NEW YORK

IN his excellent review of myocarditis in 1941, Saphir[7] emphasizes the large number of diseases in which inflammatory lesions of the myocardium are encountered by the pathologist, in contrast to the relative rarity with which antemortem diagnosis is established.

Today myocarditis is an unpopular diagnosis because of its unguarded employment by an earlier generation who sought an anatomical explanation for all evidences of altered physiology to which the heart is spectacularly liable. Speaking of this abuse of diagnostic criteria, Sir Thomas Lewis[4] states that in his opinion the clinical recognition of myocarditis can hardly be established except in rheumatism, and that in such instance he favors using the more inclusive term, "carditis" because pericardium and endocardium are rarely untouched when the myocardium is involved.

By inference it became accepted practice to diagnose rheumatic myocarditis when the more readily recognizable clinical signs of endocardial or pericardial disease were present. When the electrocardiographic criteria of acute rheumatic myocarditis were described,[1] early and accurate diagnosis was materially advanced, especially when it became possible to differentiate acute pericarditis[9] with some degree of surety.

Gradually the worth of similar electrocardiographic criteria has been recognized in the study of myocarditis in diseases other than rheumatic fever. Published reports suggest that acute myocarditis is not an uncommon complication of acute systemic infection, and rheumatic fever is no longer considered unique in this respect. In the growing list, meningococcus infection is a notable omission.

Saphir[8] states that in his opinion meningococcus myocarditis is common in cases who succumb to the infection. If this is true, the diagnosis is as commonly missed by physician as by pathologist. Hartwell[2] reported on a case of myocarditis with postmortem findings and at that time was able to find 12 other such cases in the literature. A recovered case of meningococcemia with myocarditis proved by electrocardiography has been recently reported.[5] It has occurred to us that cases suffering from acute myocarditis due to meningococcus may sometimes be confused with the currently popular hypo-

* Department of Pathology, University of Wisconsin Medical School. Madison, Wisconsin

adrenal syndrome (Waterhouse-Friederichsen), and that the differentiation is of utmost importance. Meningococcus infections are prevalent during the present war, but effective new therapeutic agents have reduced the mortality, thus opening a new field involving the medical care of those cases which recover. It is therefore, with a view to better understanding and treatment of such survivors, that 2 cases are being reported in some detail.

Case Reports. CASE 1. A white male, 23 years of age, was admitted to hospital complaining of sore throat, cough and headache of 36 hours duration. Physical examination revealed inflammation of the nasopharynx, enlarged tonsils, a few moist râles at the base of the right lung, and an appearance of toxicity out of proportion to these findings and a fever of 99.8° F. (M).

Although the skin was normal on admission, multiple, small, purpuric lesions developed within 3 hours. The temperature rose, tachycardia appeared, headache increased, and definite nuchal resistance became apparent. The spinal fluid contained 1900 white cells per c.mm. and meningococci were cultured from it. The organisms were also grown from the blood at this time. The total white blood cell count was within normal limits but rose to 41,000 the day after admission.

Sulfadiazine was immediately commenced when the diagnosis of meningococcic septicemia and meningitis became apparent, 3 hours after admission. The patient was given 5 gm. intravenously and 12 gm. orally during the first 24 hours, following which the concentration of blood sulfadiazine had reached 23.7 mg. per 100 cc. Sulfadiazine was omitted for the next 3 days because of renal failure associated with circulatory collapse to be described below. The sulfa concentration in the blood did not fall perceptibly until circulatory improvement, evident on the 5th hospital day. Sulfadiazine was again given and continued in gradually decreasing doses for 3 weeks, or until the 23rd day of the patient's illness. The blood sulfa level was maintained between 13 and 23.7 mg. % (daily determinations) between the 3rd and 10th day of illness, and consistently below 13 mg. %, thereafter. A total dosage of approximately 125 gm. of sulfadiazine was given.

A minimum urinary output volume of 1500 cc. per 24 hours was maintained except during the period of oliguria mentioned. While he was conscious and able to swallow, sufficient sodium bicarbonate was given to alkalinize the urine.

Despite immediate chemotherapy the patient had a stormy course. The neck rigidity increased, he became semiconscious and developed bowel and urinary incontinence. The purpura increased and coalesced until no part of the body was free of lesions, superficially, except for the left fifth toe which developed gangrene of its tip. There were severe bilateral subconjunctival ecchymoses and large herpetic bullæ on the lips.

After admission the patient went into circulatory collapse. Blood pressure fell from 100/60 to 80/40. The pulse rate was rapid and of poor quality; respirations were rapid and shallow; he vomited and there was well marked dependent edema, especially about the ankles. It was difficult to distinguish the extravasations of blood from edema, especially around the eyelids. Blood non-protein nitrogen had increased to 66 mg. %. This phase (circulatory collapse) was treated successfully by routine anti-shock measures including blood plasma. Adrenal failure was hypothecated and cortical extract would have been added to the therapy, had it been available. It was several days before normal renal function reappeared, the interval being characterized by low blood pressure, oliguria, peripheral edema, elevation of N.P.N., and slow excretion of sulfadiazine.

The neck became flaccid late on the 3rd day of illness but fever continued and convalescence was slow. The fever reached approximately 102° F. (R) daily for 10 days and 100° F. for 14 additional days. Severe headaches were recurrent. He lost a total of 25 pounds in weight and was troubled by numerous ulcers from necrosis of the larger purpuric lesions.

The prolonged fever was reason for continuous concern. In retrospect, it seems unlikely that the meningococcus organisms were viable throughout. It seems more probable that the secondary effects of infection, *i. e.*, tissue destruction, extravasation of blood into the tissues, toxicity and general debility, were responsible.

The heart did not attract attention except during the period of low blood pressure and

circulatory collapse when the rate was rapid and the sounds were of poor quality with occasional irregularity of rhythm. After the 5th day of illness, nothing untoward was noted and electrocardiograms were taken. On the 28th day he was allowed up gradually about the ward. This he seemed to tolerate very well, but activities were necessarily limited by reason of the gangrenous toe, described above.

On the 33rd day of illness he complained of slight nausea and of his heart "skipping beats." He was put to bed, the pulse became regular, and nausea was relieved. He slept well that night. The following morning (0630 hours), he had what the ward attendant described as a "convulsion." The nurse found him cyanotic, "pulseless and dyspneic." Resuscitation was unsuccessful and the patient was pronounced dead at 0650 hours.

Necropsy (by Capt. R. A. Kritzler, M.C.). Army Medical Museum Acc. No. 111870.

Exterior: There were brown purpuric areas in the skin that measured from 0.5 to 0.8 cm. across.

Pleural cavities: Both were obliterated by fibrous adhesions.

Heart: Weight 310 gm. The right atrium and ventricle were slightly dilated. The epicardium, endocardium and heart valves were normal. The outer 0.2 to 0.3 cm. of the myocardium over all chambers and the septum was a light brown color, glistening and soft in striking contrast to the light red underlying muscle.

Lungs, spleen, liver and kidneys were normal.

Suprarenals: The left was somewhat smaller than normal but otherwise there was no evident gross abnormality.

Gastro-intestinal tract: There were small petechial hemorrhages in the rugæ of the gastric mucosa.

Brain: Weight 1270 gm. There were small opaque areas in the leptomeninges over both cerebral hemispheres.

Microscopic examination: The section through the outer part of the left ventricle is illustrated in Figure 1. The epicardium, subpericardial adipose tissue and branches of the coronary arteries are normal. A sharply demarcated outer zone comprising nearly one-third of the myocardium, is virtually devoid of muscle fibers, the stroma is collapsed and the small capillaries lie close together. There is infiltration with a few lymphocytes and monocytes, many of the latter containing phagocyted yellow amorphous pigment. Scattered within this area are a few faintly stained swollen and vacuolated muscle fibers. This is most conspicuous at the junction of normal and degenerated tissue (Fig. 2). In none of these areas is there proliferation of fibrous tissue.

In the myocardium are small widely disseminated areas of edema, capillary engorgement and degeneration characterized by loss of, or pyknosis, of nuclei, and swelling or complete absence of muscle cells (Fig. 3). In some places only bundles of myofibrils remain. Evidence of inflammation is conspicuously absent and the intramural arteries and arterioles are normal. The muscle fibers near the endocardium are pale and swollen, but for the most part the striations remain. A section through the interventricular septum is similar and the alteration is most marked in the subendocardial fibers. Adjacent to the conduction bundle is an elongated mass of fused, swollen, pale staining muscle cells, elsewhere are large focal occasionally perivascular areas of degeneration.

A section through the right ventricle was similar, but the degeneration was more patchy.

Suprarenal: In both the reticular and fascicular zones, partial or complete loss of cortical cells, collapse of the reticular network and dilation of the sinusoids is noted (Fig. 4). Large numbers of phagocytes are filled with iron-containing pigment.

Case 2. A white male, 24 years of age, was admitted to hospital approximately 36 hours after the sudden onset of chills, fever, headache, and pains in knees and elbows. On admission he was stuporous; his temperature was 104.2° F., pulse 120, and respiration 28 per minute. He had an extensive fine purpuric rash over the skin, and ecchymoses of the mucous membranes of the soft and hard palate, and subconjunctivæ of both eyes. There was definite stiffness of the neck. The spinal fluid contained 412 white cells per c.mm. and gram-negative diplococci were seen in the direct smear, but did not grow in culture. Meningococci were grown from the blood culture. The leukocyte count was 16,600.

Sulfadiazine was started at once, both intravenously (5 gm.) and by mouth. On the following day (3rd of illness) the blood

level was 10.5 mg. %. Thereafter reasonably good concentrations were maintained with difficulty on adequate dosage. During the subsequent 9 days the average level was 8 mg. %, with a maximum of 12.7 and minimum of 2.5 mg. %.

During the first 24 hours in hospital the patient was very ill and an early Waterhouse-Friederichsen syndrome was then suspected. Hourly blood pressure readings were taken. The lowest recorded was 87/45. With it circulation was fully maintained.

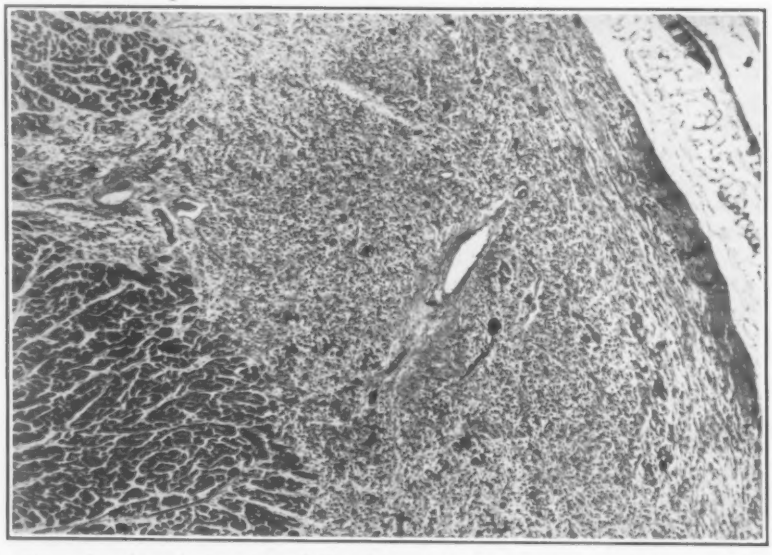


FIG. 1.—A section through the pericardial surface of the left ventricle. Practically all the muscle fibers have disappeared and an area of degeneration is infiltrated with lymphocytes and monocytes. × 50. (U. S. Army Medical Museum Neg. No. 82567.)

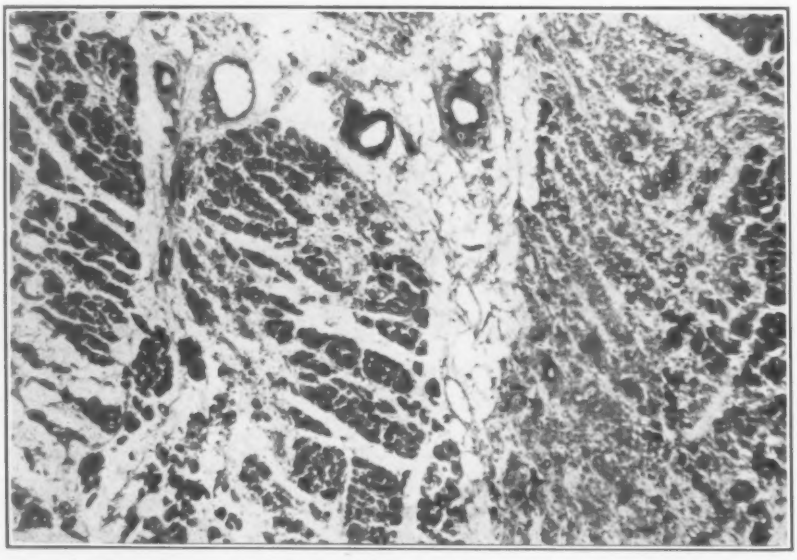


FIG. 2.—A section from the margin of an area of degeneration. × 120. (U. S. Army Medical Museum Neg. No. 82570.)

On the 3rd day of illness he commenced to improve, rapidly became oriented, and all signs of meningeal irritation disappeared.

On the 4th day, the heart sounds were of poor quality, and largely because of experience with Case 1, an electrocardiogram was taken (Fig. 5).

The purpuric rash reached its peak on the 5th day of illness and from then onward an occasional new lesion was noted but the rash as a whole faded as he continued to improve.

On the 8th day he complained of pains in both wrists which were slightly swollen. The next day, the left elbow and left knee

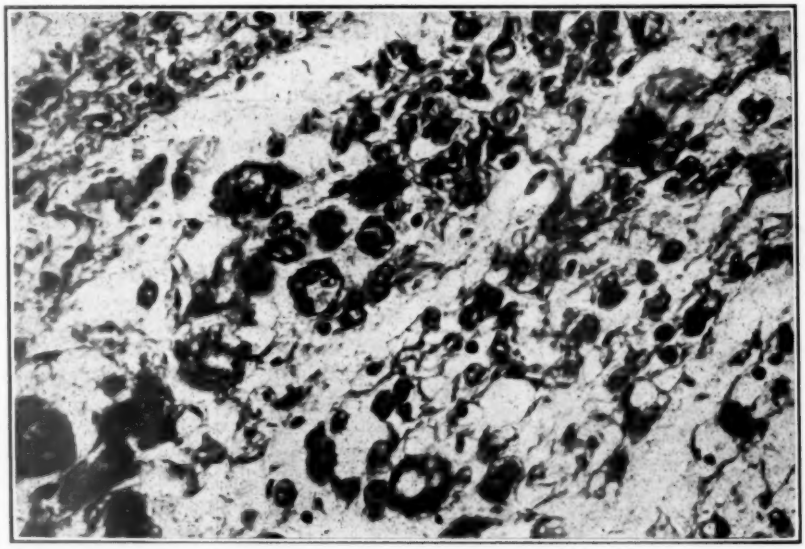


FIG. 3.—A higher magnification to show muscle degeneration. × 705. (U. S. Army Medical Museum Neg. No. 82564.)

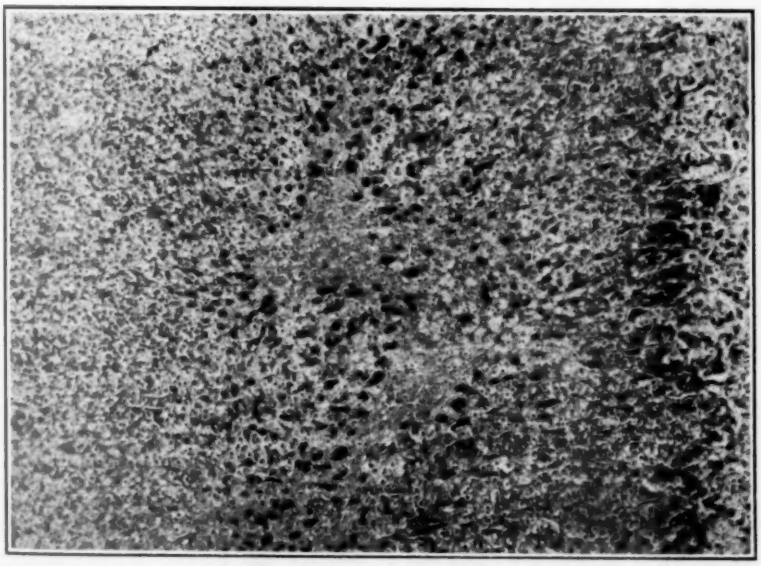
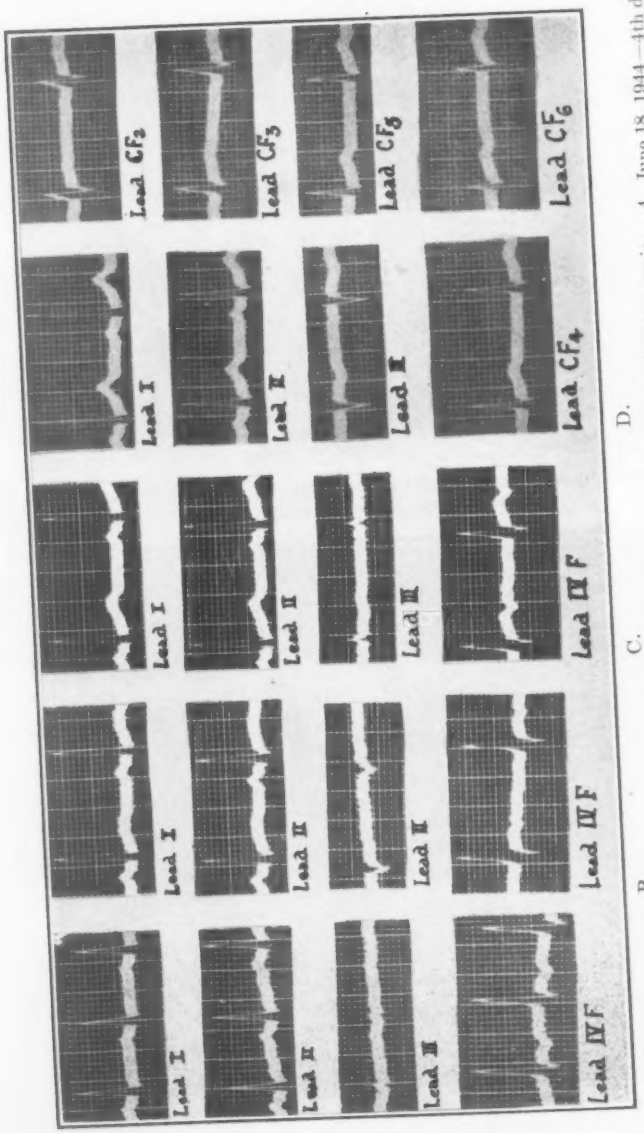


FIG. 4.—A section of suprarenal to illustrate degeneration of cortical cells and dilatation of sinusoids. × 700. (U. S. Army Medical Museum Neg. No. 83213.)

were worse, and he had sharp pains in both eyeballs. The retinal fundi were normal and the media clear. By the 11th day, the left elbow was considerably swollen, the white blood count which had subsided returned to 15,000 per c.mm., and there was low-grade fever. Sulfadiazine was discontinued at this time because the patient was no longer responding favorably to it.

He was treated symptomatically and observed for the ensuing 36 hours. The temperature rose to 101° F. and he developed a heavy fresh maculopapular, salmon-colored rash frequently associated with chronic low-grade meningococcemia. There was no recurrence of purpuric phenomena. The left elbow was aspirated, but only a few drops of clear sterile fluid was obtained. A blood culture was also reported sterile.

Clearly meningococcemia was still present,



A. B. C. D.

FIG. 5.—Selected serial electrocardiograms, Case 2, taken during course of acute meningococcemia. *A*, June 18, 1944—4th day of illness. Sinus tachycardia, rate 124 per min. P–R, 0.16 sec. QRS, 0.08 sec. Note the isoelectric T waves, Lead I, diphasic Leads II and III, and negative Lead IV F. *B*, June 21, 1944—7th day of illness. Sinus rhythm, rate 88 per minute. P–R, 0.16 sec. QRS, 0.08 sec. Note that the T waves are now positive in Lead I (notched) and Lead II; diphasic Lead IV F. *C*, June 25, 1944—11th day of illness. Sinus rhythm, rate 70 per min. P–R, 0.16 sec. QRS, 0.08 sec. Note further improvements in T waves. *D*, August 22, 1944—69th day of illness. Sinus rhythm, rate 86 per min. P–R, 0.16 sec. QRS, 0.08 sec. Earlier records of Lead CF_6, the T waves had been negative. The T waves in Lead III have become negative. The additional precordial leads are included.

but no longer fulminating. It seemed probable that this was an *in vivo* exhibition of meningococcus-acquired sulfonamide resistance,[3] in this instance contributed to by a lower blood concentration than optimum during a 9 day course of sulfadiazine. There were in addition, signs of moderate sulfonamide lithiasis so the therapy was changed. Penicillin injections (25,000 units every 2 hours, intramuscularly) were given with immediate and permanent cure of infection. A total of 650,000 units of penicillin was used.

The cardiac sounds progressively regained strength and tone after the 4th day of illness. On the 8th day a soft blowing systolic murmur appeared at the pulmonary area and apex. It persisted and had the characteristics of a functional pulmonic murmur. On the 23rd day of illness the patient became aware of "skipping" of the heart. He was at bed rest and under no unusual stress. No arrhythmia was found. Frequent electrocardiograms taken during the patient's stay in hospital showed acute type serial changes in the terminal segments of the ventricular complexes. Selections from these tracings are reproduced in Figure 5. The cardiac silhouette was normal on each of several roentgenologic examinations.

Physical activity was restrained long after the patient had symptomatically recovered, chiefly because the electrocardiographic pattern was slow to stabilize and the erythrocyte sedimentation rate continued to be slightly elevated. He was allowed up gradually on the 61st day of illness, and from thence onward had an uneventful convalescence. When last heard from, 5 months after onset of his illness, he was being sent to full duty. A recent electrocardiogram is said to be normal but is not available for comparison with our series.

Discussion. Acute myocarditis occurs in meningococcus infection, although only a small number of cases are recorded.[2,5,8] It is sometimes associated with endocarditis, but the type under consideration occurred without involvement of endocardium and pericardium.

Saphir[7,8] describes the histology of meningococcus myocarditis as: (1) hemorrhagic exudation, (2) early appearance of endothelial leukocytes, (3) destruction of muscle fibers, and (4) presence of intracellular Gram-negative diplococci. It is important that all his cases died during an active phase of infection. This accounts for the presence of organisms in the muscle, and also indicates the severity of the infection in which acute myocarditis is known to have developed.

Toxemia and severe systemic infection were clinical features in both of our cases, and as pointed out, have likewise been conspicuous in recorded cases. Damage to the heart fibers adjacent to the conduction bundle is worthy of note since it seems fair to assume that it may have contributed directly to the unexpected death of this soldier. Saphir[8] noted a similar location of damage in some of his cases and speculated upon its importance.

Because of the high blood concentration and the unusually long duration of sulfadiazine therapy in Case 1, the possible toxic effects of the drug on heart muscle must be considered. However, no lesions suggestive of drug damage were found in other viscera, and sulfonamides tend to cause a diffuse myocarditis rather than localized degeneration. Also myocarditis occurred in meningococcus infections prior to the discovery of sulfonamides; in our second case, it occurred with relatively low blood sulfa concentrations.

To obtain information on the incidence, of meningococcus myocarditis, electrocardiograms were taken on a series of 8 cases. One or more tracings were taken between the third and fifth days, the period when changes were noted in Case 2, and compared with a control taken after full recovery. Several of the cases had severe epidemic meningitis, two were comatose, but none exhibited signs of fulminating septicemia. No electrocardiogram deviated significantly from normal. Since one of the distinguishing signs of fulminating septicemia is severe toxemia and acute myocarditis occurs most frequently in such cases, it seems probable that meningococcus toxin may be of importance.

As regards the incidence of meningococcus myocarditis, the supposition that it occurs chiefly in cases of fulminating

septicemia automatically imposes limitations since these cases are rare when compared with the total number infected. Within the group liable to the complication clinical experience (D. V. H.) leads us to suspect it may be relatively high, since these are the only 2 cases of fulminating septicemia seen during 2 years in a large hospital installation in the European Theater of Operations, where meningococcus infections were continuously encountered. On review of 29 autopsies on cases of meningococcus infection studied in this theater a lower incidence was found (D. M. A.). The heart was recognized as the cause of death in only 1 individual (Case 1) when no more than routine examination of the heart (gross and microscopic) had been made. Nevertheless 7 of 29 showed some noteworthy degree of acute myocarditis. Seventeen of the group died with fulminating septicemia, and 12 predominantly with meningitis. Six of the 7 cases with myocarditis occurred in association with septicemia whereas only a single case appeared among the remaining 12. This was similar to Saphir's observation of a 20% incidence in a group of 10 autopsies. It is clear that further observations, anatomical as well as clinical, are necessary to assess the expected incidence of meningococcus myocarditis but on the basis of known facts, it is apparent that it occurs more often than is generally appreciated.

The phenomenon of circulatory collapse, or shock (Waterhouse-Friederichsen syndrome), is a well recognized entity which occurs in cases of fulminating septicemia. It is popularly supposed to be directly caused by adrenal failure, because the cases resemble Addisonian crises and because both adrenal glands are often destroyed by hemorrhage. The explanation is not entirely satisfactory. Onset of the syndrome in humans is usually rapid, often within a few hours of onset of illness, while laboratory animals with bilateral cortical extirpation develop symptoms after 48 or more hours, and Rogoff and Stewart[6] report 7 days average survival of dogs after adrenalectomy. Whereas small fragments of cortical tissue are sufficient to maintain life in animals, collapse and death in humans are observed without corollary evidence of gland injury. The depression of blood pressure, urinary suppression, hemoconcentration, and elevation of nitrogenous waste in the blood, are common in so-called surgical shock, and not necessarily dependent upon reactions of either adrenal glands or liver. The adrenal histology in our case suggests unilateral damage which probably occurred during the acute infectious phase, but whether or not it was functionally significant, we are unable to determine. It is probable that the myocardial damage may have contributed more than the adrenal damage, and that the observed fall in blood pressure could have been wholly explained by reduction of cardiac output.

Although it is well known that acute heart failure may be indistinguishable from peripheral vascular failure the recognition of myocarditis is of great importance for the selection of proper therapy. Differentiation would be of negligible practical importance were it not for the fact that indications for treatment are different. Measures taken to increase circulating blood volume in the one, may prove fatal in the other. Case 1 responded to therapeutic trial as one would expect in peripheral vascular failure, which has some weight as regards the mechanism in that individual case. On the other hand the coëxisting myocardial damage was an unsuspected element, and it was fortunate the therapeutic procedures undertaken were within the functional capacity of the damaged organ.

Convalescent care in meningococcus myocarditis is the other important consideration. The primary objective of convalescence is the repair of the damaged tissues and intelligent planning presupposes full recognition of the extent of this damage. In Case 2 treatment was planned to reduce cardiac work to a minimum, over a sufficiently long period to allow

healing. The optimum time for bed rest needs to be determined on a larger series of cases, but on the basis of these 2 cases a minimum of 6 weeks is believed desirable. This period is suggestively similar to the average duration of myomalacia following myocardial infarction. Hyperirritability of the heart as indicated by awareness of cardiac irregularity in both cases merits special consideration, and may occur as late as the fifth week of illness. The common prophylactic measures, including quinidine, should be employed.

Summary and Conclusions. 1. Two cases of meningococcus myocarditis are presented. Both had fulminating septicemia, one with definite signs of circulatory collapse (Waterhouse-Friederichsen syndrome), the other without.

2. The diagnosis of acute myocarditis was proven in 1 case by anatomic examination following a cardiac type death on the 33rd day of illness. The soldier had been treated with sulfadiazine for his infection, which was cured, and had survived early circulatory collapse as well.

3. The diagnosis of acute myocarditis was suspected in the second case because of clinical observation and experience with Case 1. An electrocardiogram on the fourth day of illness showed important changes. The serial electrocardiograms are reproduced and other findings associated with convalescence described.

4. It is believed that the myocardial damage was not a result of sulfonamide toxicity.

5. Clinical recognition of acute myocarditis will be facilitated when its association with fulminating meningococcemia, is appreciated. Diagnosis is critically important early in the disease when signs of circulatory collapse supervene in planning convalescence.

6. A tendency to cardiac arrhythmia occurring as late as the fifth week of illness should be kept in mind and prophylactic precautions should be undertaken when there is evidence of hyperirritability of the heart.

The interest and inspiration of Col. William S. Middleton, M.C., A.U.S., in preparation of this manuscript is gratefully acknowledged.

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SPONTANEOUS PNEUMOTHORAX IN HEALTHY YOUNG ADULTS

WITH PARTICULAR REFERENCE TO THE ETIOLOGICAL RÔLE OF AERIAL ASCENT

BY CAPT. ERLE M. HEATH, M.C.
PITTSBURGH, PENNSYLVANIA

RECENTLY considerable interest has been manifested in the rôle of ærial ascent in precipitating spontaneous pneumothorax. Holter and Horwitz[4] reported a case of spontaneous pneumothorax apparently precipitated by ascent to 8000 feet in an airplane. Lovelace and Henshaw,[7] Todd,[13] and others have described the effect of aerial ascent on patients with preëxisting pneumothorax. During the past year, 2 cases of spontaneous pneumothorax incident to altitude chamber flights were observed. One of these occurred during the flight; the other was present prior to the flight but symptoms were aggravated by the flight. It is the purpose of this paper to present these cases along with data concerning the incidence of spontaneous pneumothorax occurring during altitude chamber flights.

Incidence. In this study, the records of 86,916 man-flights in the altitude chamber were surveyed for the occurrence of spontaneous pneumothorax. The subjects were healthy, young combat bomber crew members. The "flight" consisted of a training flight of 90 minutes duration ascending from ground level (atmospheric pressure approximately 700 mm. Hg) to a simulated altitude of 30,000 feet (pressure 225 mm. Hg). The rate of ascent was approximately 2000 to 3000 feet per minute; peak altitude was maintained for approximately 15 minutes. In these 86,916 man-flights, spontaneous pneumothorax occurred in only one instance. In one other subject, symptoms due to a preëxisting partial pneumothorax necessitated descent from 17,000 feet.

A further survey was made of 771 individuals undergoing an explosive decompression "flight." This involves a change of altitude from 8000 feet (564 mm. Hg pressure) to 20–23,000 feet (349–307 mm. Hg pressure) in less than 1 second, and simulates the effect of decompression by gunfire or flak of a pressurized cabin aircraft flying above 20,000 feet. In these 771 man-flights there was no instance of spontaneous pneumothorax. These findings are in accord with most data published to date on "explosive decompression." Sweeney[12] reported no evidence of pathological changes in explosive decompression of human subjects. Recently, however, Clark[2] reported 2 cases of mediastinal emphysema following explosive decompression of human subjects from a simulated altitude of 8000 feet to a simulated altitude of 31,000 feet in 0.5 second.

For purpose of comparison, a survey of the incidence of spontaneous idiopathic pneumothorax as compiled from the literature and the clinical records of the AAF Regional Hospital, Lincoln, Nebraska, was made. The term idiopathic spontaneous pneumothorax is applied only to those cases occurring in individuals in apparent good health with no evident pulmonary disease. Those cases secondary to some recognized underlying pulmonary disease such as tuberculosis or bronchial asthma are not included in this category. Jones and Gilbert[5] in 1936 collected 19 cases of idiopathic pneumothorax recorded prior to that time. Babington[1] in 1944, reported 44 cases of idiopathic spontaneous pneumothorax, 31 of which were from the literature from 1935 to 1940. In a review of approximately 50,000 examinations of the chest Santos and Tanchanco[10,11] found only 57 cases of idiopathic spontaneous pneumothorax, an incidence of only .11%.

A survey of 28,000 admissions to AAF Regional Hospital, Lincoln, Nebraska, revealed 10 cases of spontaneous idiopathic pneumothorax (including the 2 herein reported); all were confirmed by Roentgen

ray. Of these 10 cases, 1 occurred during altitude chamber flight, 1 during sleep, 2 during walking, 1 while getting out of bed, and 1 while sitting at a desk; the activity of the remaining 4 patients was not recorded. In none of these individuals was there any evidence of tuberculosis, bronchial asthma, emphysema or other pulmonary disease. In 7 of the 10, there was no previous history of any pulmonary disease. Three gave a past history of "pleurisy" (2 with single episodes 3 years previously—1 with recurrent episodes for the preceding 6 years). The degree of collapse of the affected lung varied from 20% to 100%. All patients recovered with complete reëxpansion of the lungs in from 3 to 6 weeks. The duration of hospitalization varied from 16 to 56 days; the average stay was 32 days.

From these data, it would seem logical to conclude that changes of altitude encountered in normal aerial flight have no appreciable bearing on the precipitation of spontaneous pneumothorax in individuals with no apparent preëxisting lung disease. The occurrence of spontaneous pneumothorax during normal aerial flight is so rare that it is of no practical significance, and the impression that normal aerial flight is likely to produce spontaneous pneumothorax in a healthy individual is an erroneous one. The relationship between pneumothorax or pneumomediastinum and "explosive decompression" requires further study.

Case Reports. Case 1. Pfc., aerial gunner, white, age 19.

History. This patient was admitted to the hospital Feb. 13, 1945, complaining of pain in the lower right chest. He stated that he was well until February 10. On that day while in the altitude chamber at 15,000 ft. he noticed the onset of moderate pain in the lower right chest aggravated by deep breathing and accompanied by moderate dyspnea. The patient was then descended to ground level in the lock, and the pain persisted for several hours. The following morning the pain had completely disappeared, and there was no recurrence on February 11 or 12. On February 13 the patient again took an altitude chamber flight. At 18,000 ft. during ascent he noticed an aching pain in the lower right chest and again requested descent. Descent was begun at 18,000 ft., and the patient's symptoms disappeared completely at 17,000 ft. He had no pain after that time. He gave no history of diseases of the lungs or any previous serious illness or operation. Family history was irrelevant; there was no history of contact to tuberculosis.

Physical Examination. At the time of admission, physical examination revealed a thin, white male, not acutely ill, suffering no marked respiratory distress at the time. Pulse was 85 per minute, regular, and normal volume. Blood pressure was 118/83. Physical examination was negative except for lung findings as listed below.

Lungs: No lag or limitation of respiration was noted. There was slight decrease of tactile fremitus on the right side posteriorly. Percussion note was hyperresonant over the right side, both anteriorly and posteriorly. Normal vesicular breath sounds were heard over the entire left chest. Breath sounds were absent over the right chest anteriorly. Posteriorly, hollow tubular breath sounds were heard in the lower right chest near the midline. There was an absence of breath sounds over the remainder of the right chest. Egophony was noted over the same area as the tubular breathing.

Roentgen Ray Examination. Roentgen ray on February 13 showed typical partial pneumothorax of the right chest (Fig. 1). The lung was approximately 60 to 75% collapsed; there appeared to be some thickening of the bronchovascular markings on both sides. There was only slight displacement of the heart and mediastinal contents toward the left side.

Progress. The patient was kept at bed rest and was observed by physical examination and repeated Roentgen ray studies. By February 19 physical and Roentgen ray examination showed that the lung had begun to reëxpand (Fig. 2). On February 27 Roentgen ray examination showed approximately 85 to 95% reëxpansion of the lung. On March 9 normal vesicular breath sounds were heard over the entire right chest, and Roentgen ray examination showed complete reëxpansion of the right lung (Fig. 3). During this period of hospitalization, the patient remained symptom-free at all times. Blood

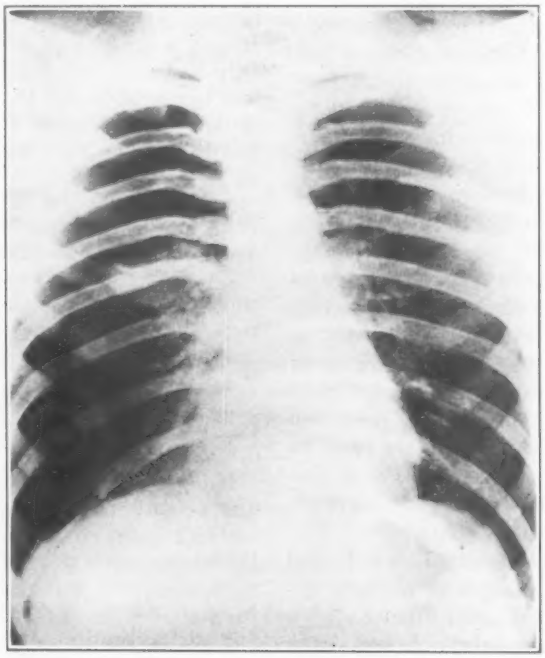

FIG. 1.—Day of admission, February 13. Shows partial pneumothorax on right side.

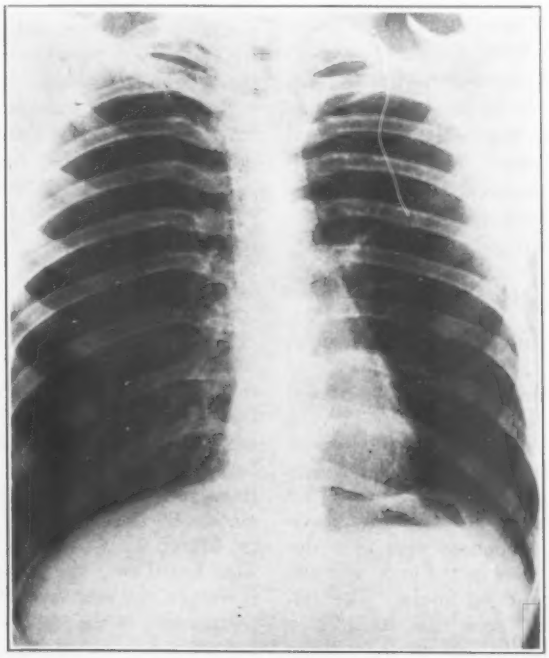

FIG. 2.—February 19, 1945. Shows beginning of reëxpansion of right lung.

count, urinalysis, sedimentation rate and tuberculin test were normal.

CASE 2. Cpl., aerial gunner, age 19.

History. This patient was admitted on June 17, 1944, complaining of shortness of breath and pain in chest occurring during an altitude chamber flight the previous day. He stated that during ascent at 10,000 ft. he suddenly noticed difficulty in breathing and acute pain throughout the left chest. He gave a past history of having pneumonia 4 times as a child and being bothered with "pleurisy," especially on the left side, for the past 6 years. For 1 week prior to hospitalization the pain was localized in the left chest, and the patient had a chest Roentgen ray on June 12. This Roentgen ray showed partial pneumothorax on the left side and some pleural adhesions at the left base. The patient, however, was not aware of any abnormality prior to his chamber flight. He states that he was told that his chest Roentgen ray was negative. At any rate, the patient was permitted to make an altitude chamber flight on June 16 when a partial pneumothorax was noted on Roentgen ray on June 12.

Physical Examination. On admission, physical examination was negative except for the chest findings as follows: There was a slight lag in the left chest. A friction rub was heard in the left axillary area and decreased breath sounds and increased resonance noted on the left chest laterally.

Roentgen Ray Examination. Roentgen ray on admission revealed a partial pneumothorax of the left side, the left lung being collapsed about 25%. There were some diaphragmatic adhesions. The right lung field was clear.

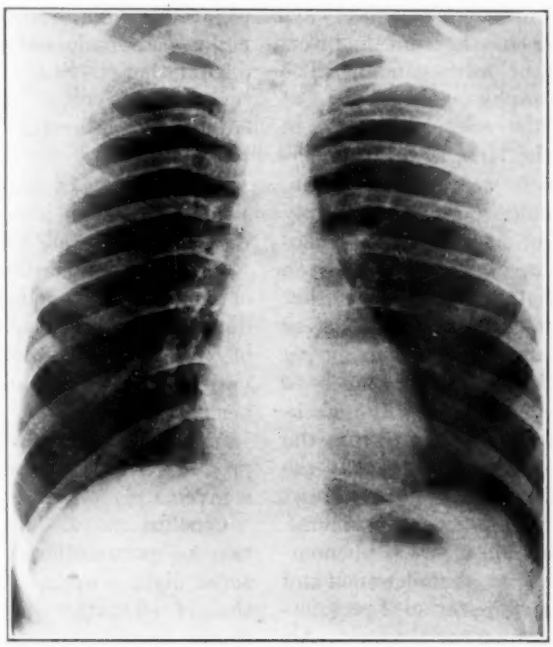

FIG. 3.—March 9, 1945. Shows complete reëxpansion of right lung.

Progress. During hospitalization the patient was treated symptomatically and kept at bed rest. The dyspnea and pain rapidly disappeared. The patient felt well during his period of hospitalization. On June 26, 1944, Roentgen ray examination showed that the pneumothorax on the left side was reëxpanded. The diaphragmatic adhesion still remained. Repeated sedimentation rates were normal. Repeated sputum examinations were negative for tubercle bacilli. Tuberculin skin test was negative and patient was discharged to duty on July 1, 1944.

Comments. The first of these cases illustrates a type of idiopathic spontaneous pneumothorax, apparently precipitated by simulated aerial flight. The mechanism of this phenomenon is not well understood. Common explanations of the mechanism of spontaneous pneumothorax are: (1) Rupture of an emphysematous bleb, or (2) Rupture of the visceral pleura. More recently Hamman[3] has suggested that the initial lesion may be "interstitial emphysema of the lungs with an escape of air to the pleura through the mediastinum." Macklan[8] has demonstrated air pathways along the vascular sheaths from the interstitial tissue to the mediastinum. The rupture of an emphysematous bleb at altitude due to the relative increase in pressure within the bleb, is easily understood. If such blebs were at all common, however, one would expect considerably higher incidence of spontaneous pneumothorax during aerial flight than that given above. It is difficult to see why the other mentioned mechanisms should be more common during aerial flight than during other activity. Certainly, we do not have sufficient data to speculate on the mechanism in this particular case. From the data presented, it seems likely that the occurrence of spontaneous pneumothorax during aerial flight is merely coincidental.

The second case illustrates a phenomenon which is much better understood and described—that of aggravation of preëxisting pneumothorax upon aerial ascent. Air within the pleural cavity responds to Boyle's law during ascent. The volume of this air will vary inversely with the absolute pressure of the atmosphere; or, if the volume remains stationary, the pressure exerted by this entrapped air will be increased. Therefore, a given degree of pneumothorax at ground level will produce progressively increasing degrees of lung collapse during ascent. This has been well shown by clinical and radiographic observation during altitude chamber flights,[9,13] and its importance in aerial transportation of chest injuries pointed out.[7,13] Todd[13] on a basis of fluoroscopic and Roentgen ray examinations at various altitudes has recommended that no person with pneumothorax ascend above 4000 feet. Lovelace and Henshaw[7] have pointed out that the severity of symptoms of pneumothorax depends on the pressure involved and volume of the air in the pleural cavity; these, of course, vary with altitude.

Summary. 1. The records of 86,916 man-flights in altitude chambers were reviewed, revealing only 1 case of spontaneous pneumothorax.

2. Seven hundred and seventy-one "explosive decompression" altitude chamber flights were conducted with no incidence of pneumothorax. Study of the literature revealed 2 reported cases of mediastinal emphysema following "explosive decompression."

3. In a series of 28,000 hospital admissions, 10 cases of idiopathic spontaneous pneumothorax were found.

4. Two case records are presented: One of spontaneous pneumothorax occurring during a simulated aerial flight, and one of preëxisting pneumothorax with aggravation of symptoms during altitude chamber flight.

5. Discussion of possible mechanism of production of spontaneous pneumothorax is given.

Conclusions. 1. The incidence of spontaneous pneumothorax during simulated aerial flight is apparently no greater than that of idiopathic spontaneous pneumothorax occurring during other activities.

2. The common impression that spontaneous pneumothorax is likely to be caused by normal aerial ascent is an erroneous one, not supported by factual data.

3. The occurrence of spontaneous pneumothorax during normal aerial flight in individuals with no definite preëxisting lung disease is not common enough to be of practical significance.

4. In individuals with preëxisting pneumothorax, symptoms will be precipitated or aggravated by aerial flight. Such individuals should avoid flying, or if flying is necessary, should be restricted to low altitudes.

5. Spontaneous idiopathic pneumothorax in young adults is not of serious prognostic importance; complete reëxpansion of the collapsed lung usually occurs in 4 to 6 weeks.

6. The relationship between pneumothorax or pneumomediastinum and "explosive decompression" requires further study.

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WHY CERTIFIED MILK?*

By J. Howard Brown, Ph.D.
ASSOCIATE PROFESSOR OF BACTERIOLOGY
BALTIMORE, MD.

(From Johns Hopkins University School of Medicine)

Why ask this question? This is not an argument for or against pasteurization, but I do hope to show that pasteurization is not the entire solution of the milk problem and that there are many reasons why certified milk is superior to other grades of milk on the market.

The fiftieth anniversary of Certified Milk† passed unnoticed in 1943. Its history is related in the first pages of Methods and Standards for the Production of Certified Milk. Throughout this period only 3 outbreaks of human disease have been attributed to Certified Milk: 1920, White Plains, N. Y. (diphtheria); 1924, New Rochelle, N. Y. (paratyphoid); 1926, Hamden, Conn. (septic sore throat). Perhaps as a result of these experiences and constant improvement in Methods and Standards for the Production of Certified Milk‡ there have been no outbreaks of disease attributed to certified milk since 1926. Previous to 1925 the public health reports of milk-borne disease are not very satisfactory. In this year the U. S. Public Health Service Milk Ordinance began to be adopted by various communities. Also since 1925 we have a complete file of Reports of Disease Outbreaks Conveyed through Milk and Milk Products in the United States as issued by the U. S. Public Health Service. It is from these reports that our statistical information has been obtained. The report for 1944 is not yet available.

During 19 years (1925–1943) there have been reported 819 milk-borne outbreaks, including 25 listed as "possibly conveyed through milk or milk products," an average of 43 per year. The maximum was 68 in 1926; the minimum 33, in 1932. Classified according to the kind of disease, the outbreaks were as follows:—

Typhoid fever	391
Gastro-enteritis and food poisoning	183
Streptococcal	184
Brucellosis	31
Dysentery	15
Diphtheria	15
	819

Classified according to the kind of milk or milk product involved, the outbreaks were as follows:—

Certified (raw)	1
Other raw[1]	712
Pasteurized	62
Canned	3
Boiled	2
Unknown	39
	819

[1] Those outbreaks reported as due to both raw and pasteurized milk are included under "raw" only; there were 7 such.

In 1940 it was stated[1] that "Epidemics of the types outlined recur year after year, even from certified and grade A raw milk." . . . "Even certified raw milk has been responsible for outbreaks." In view of the statistics presented above, is this generous use of plurals and "year after year" applicable to Certified Milk? Continuing: "It is a most significant fact, however, that no outbreak has ever been reported as due to grade A pasteurized milk in any city operating under the milk ordinance recommended by the Public Health Service." The statement was carefully worded to exclude all but grade A pasteurized milk and, apparently, was based upon data available through 1938. Since then there have been 5 outbreaks

* Abstract of a talk before the Milk Commission of the Philadelphia Pediatric Society, February 20, 1945.

† These words are capitalized as the name is copyrighted in this form

‡ Methods and Standards, 1928, was the first milk control manual in which directions were published for the recognition of the hemolytic streptococci of septic sore throat.

attributed to grade A pasteurized milk in communities operating under the Public Health Service ordinance. If all kinds of milk recognized under the ordinance are considered, there have been over 60 outbreaks (12 attributed to pasteurized milk or products) since 1925. The ordinance has been in effect in 1181 communities for varying lengths of time and doubtless has been beneficial. It includes recognition of Certified Milk the public health record of which is unsurpassed by that of any other grade of milk, raw or pasteurized.

As may be noted in the first tabulation above, 93% of the reported outbreaks of milk-borne disease are of typhoid fever, streptococcal disease (septic sore throat and scarlet fever) and gastroenteritis (food poisoning). Until 1935 typhoid fever constituted more than 50% of milk-borne outbreaks. Because of the decline in the typhoid rate in the population at large due to many factors, such as improved water supplies, anti-typhoid vaccination, and increase in pasteurization of milk, typhoid constituted only 12% of milk-borne outbreaks of disease in 1942 and 1943. The incidence of milk-borne streptococcal outbreaks was above 30% in 1929, and above 40% in 1936, but has declined fairly consistently since then to 10% in 1943. Contrasted with these, the incidence of gastroenteritis attributed to milk and milk products has risen from a level of less than 15% previous to 1935 to 62% in 1943. Although this reported increase may be due to better diagnosis, especially to the recognition of staphylococcus enterotoxin as a cause of food poisoning, it is clearly established that since 1938 gastroenteritis has occupied first place among milk-borne diseases.

Udder and teat canal infections with staphylococci are very common, even in the absence of clinically recognized mastitis. Unless the dairy farm is engaged in the effort to produce raw milk of very low bacterial count, such as Certified Milk, cows harboring staphylococci are of little or no concern to the dairyman. Many of these staphylococci are indistinguishable from the enterotoxin-producing staphylococci which cause food poisoning. Milk seeded with these organisms may, by improper handling (inconstant or insufficient refrigeration), serve as culture medium in which the toxin content rises to a pathogenic level. The avoidance of such accidents is complicated by the heat resistance of staphylococci and their enterotoxin. Some strains of staphylococci survive heating at 60° C. for nearly 1 hour and it is possible to recover living staphylococci from many samples of market milk which have been pasteurized at 62° C. for 30 minutes and with negative phosphatase reactions. The enterotoxin resists heating at 95° C. for 20 minutes. From 1933 to 1943 inclusive, the U. S. Public Health Service reports record 126 outbreaks of gastroenteritis or food poisoning, excluding those attributed to chemical substances and paratyphoid organisms. Of these, 79 were attributed to raw milk or milk products, 27 to supposedly pasteurized milk or products, 1 to boiled milk, 2 to canned milk, and 17 to milk of unknown processing. In nearly half of these outbreaks staphylococci were known to be involved and in most of the others clinical evidence indicated staphylococcus enterotoxin. In many instances the dairy product was contaminated subsequent to milking, after pasteurization, or during food preparation. In other instances cows with staphylococcus mastitis were incriminated. Obviously, cows shedding staphylococci in their milk and milkers with staphylococcus infections of the hands are potentially dangerous, whether the milk is to be pasteurized or not. Undoubtedly, the time-honored broad requirements of healthy animals, healthy milkers, and cleanliness have had much to do with avoiding any outbreak of food poisoning attributable to Certified Milk.

The public has been bombarded with sensational articles in popular magazines*

* Addendum: See Raw Milk Can Kill You, Coronet, May 1945. Correspondence with the author of this article reveals that the outbreak at "Crossroads, U. S. A., in one of those states in the Midwest," was fictitious, representing no actual occurrence, and, presumably was described merely to illustrate what the author thought might happen.

creating the impression that anyone who drinks a glass of raw milk is in imminent danger of contracting undulant fever and that if all milk were pasteurized there would be no human brucellosis. Neither proposition is true. In a review of Immunity in Brucellosis Huddleson[5] (1942) has stated:

"When human beings are exposed to brucella, a large percentage of those exposed fail to show any clinical evidence of the disease, but do develop specific serum antibodies and skin sensitivity, and in some instances to the same degree as those clinically infected. . . . When antibodies or skin sensitivity are found present in healthy persons a state of active immunity is indicated."

Another factor also helps to explain the low incidence of undulant fever among consumers of milk infected with *Brucella abortus;* the dosage factor. This was beautifully demonstrated by an outbreak in an institution using raw milk from its own infected dairy herd.[4] Some of the kitchen help and others having access to an abundance of cream acquired brucellosis. Some hundreds of inmates drinking the whole (or partially skimmed?) milk suffered no ill effects. It has long been known that brucella organisms are more numerous in gravity cream than in the underlying milk. Also the dilution factor is involved in the dosage factor. In outbreaks involving fairly large milk supplies the incidence of human infection is often in the neighborhood of 1.5% of the consumers of the milk. In family outbreaks, in which all of the milk may come from a single heavily infected cow, several members may become infected.

Brucella suis is more virulent for man than is *Brucella abortus*. Hardy[2] (1943) states:

"It is still evident that in the United States the incidence of recognized brucellosis in man tends to vary directly with the extent of the hog-raising industry. . . . It was previously assumed, as a result of the studies of the Mediterranean Fever Commission, that brucellosis was acquired through the ingestion of infected raw dairy products. It has since been established through experimental study and the interpretation of epidemiological observations that the infection may readily be acquired through cutaneous contact with infective secretions, excretions, or tissues. This appears to explain the ease of infection of bacteriologists, who are generally able to avoid the ingestion of those organisms with which they work but can scarcely hope to prevent entirely the contamination of fingers and hands. The high incidence of infection in packing-plant employees is readily understood when it is known that Brucella may penetrate the normal or minutely abraded skin. Likewise the high rate of infection in men on the farm, as compared with the women, can be explained only as a result of the more common skin contamination by infective discharges of cattle or hogs."

Although hogs are resistant to *Brucella abortus*, cattle in close association with hogs occasionally become infected with *Brucella suis*. In the two milk-borne outbreaks reported by the U. S. Public Health Service (1941 and 1942) as due to *Brucella suis*, the incriminated cows had been allowed to run with infected hogs in the same lot. Reports from Iowa (Hardy, Jordan and Borts,[3] 1936) and Alabama (Annual Report, Bureau of Laboratories, Alabama State Department of Health, 1943) indicate that about 70% of human brucellosis in those states is due to *Brucella suis*. In states where there is little hog raising, more of the human brucellosis is caused by *Brucella abortus*. According to Hardy, Jordan and Borts, in the West North Central states the incidence of clinically recognized brucellosis per 100,000 population was about 4 persons and in New England less than 2. There is no reason to believe that this incidence has materially changed since 1936.

"In the case of human beings, it has been observed repeatedly in many laboratories that those who have developed an immunity as a result of a clinical or subclinical infection with one species, may

freely work with the others without becoming infected." (Huddleson,[5] 1942.)

We are confronted by a public health dilemma. The pasteurization of all milk might reduce the incidence of human brucellosis 50%; on the other hand, it might reduce the number of immunized persons in the population to such an extent that there would be an increased incidence of clinical brucellosis, especially in those occupations and regions where exposure to cutaneous infection with *Brucella suis* is a major factor. Certified Milk follows the program of eliminating brucellosis from its dairy herds and of prohibiting the mingling of cows with hogs and other animals. Under these conditions it is very improbable that an infective dose of Brucella organisms will ever gain entrance to Certified Milk.

It has been said[1] that "the one thing which differentiates pasteurization from all other protective measures is that while all other measures *may fail* to protect completely even if they are properly applied, pasteurization *will always* protect if it is properly applied." Without detracting from the value of pasteurization, 3 comments may be made: (1) Since 1926 "*other measures*" have given complete protection to the consumers of Certified Milk; (2) Pasteurization, properly applied, does not destroy some of the enterotoxic staphylococci; (3) Even with the best of intentions and equipment, pasteurization is not always properly applied. This is why it is required that Certified Milk-pasteurized must be Certified Milk before it is pasteurized; it has a double safe-guard enjoyed by no other grade of milk. Certified Milk-raw is required to have a lower bacterial count than are other grades after pasteurization. True, many samples of grade A pasteurized milk have low bacterial counts rather than counts just below the legal limit of 30,000 per cc., but how is the consumer to know which samples these are since there is nothing on the labeling to distinguish a milk with 500 bacterial colonies per cc. from one which may have a count of 30,000 per cc. unless it is certified? These are some of the reasons *why certified milk*. Others may be found in the Methods and Standards for the Production of Certified Milk, such as:

Segregation of the dariy cows from other farm animals, especially hogs.

Frequent testing of milk whey and the serum of cows for Brucella agglutinins and prompt elimination of reacting animals.

Frequent tuberculin testing of cattle.

The control of bovine mastitis.

The dairy herd under the regular supervision of a designated veterinarian.

All employees subject to weekly medical inspection by a designated physician who also makes such medical examinations and requires such laboratory tests (fecal cultures, throat cultures, etc.) as he may think advisable or as may be required by the Commission. Medical examination of all new employees.

Weekly or more frequent bacteriological examination of the milk. Control of coliform and spore-forming bacteria.

Cleanliness of the stables, milking operation, and milk-handling. Frequent inspections by a designated sanitary inspector.

There are no secret or proprietary methods for the production of Certified Milk. Any dairyman may follow the Methods and Standards but has he the facilities for doing so without the services of a Medical Milk Commission and has the public the assurance that he does so without the certification of a Commission? Is such a milk required to be produced, processed and bottled at a farm so identified on the bottle cap, or is it mixed with other milk before it reaches the consumer?

The author is very grateful to Mr. A. W. Fuchs and to the late Mr. Leslie C. Frank of the U. S. Public Health Service, who for many years have kindly supplied me with the reports discussed. I have quoted freely from my contributions to the manuscript for a book on Bovine Mastitis, A Symposium, edited by R. B. Little and W. N. Plastridge, and soon to be published by the McGraw-Hill Book Company, Inc., New York.

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AMINO ACIDS IN THE PRODUCTION OF PLASMA PROTEIN AND NITROGEN BALANCE

By S. C. Madden, M.D.
AND
G. H. Whipple, M.D.
ROCHESTER 7, N. Y.
(From the Department of Pathology, The University of Rochester School of Medicine and Dentistry)

Physicians and investigators are acutely interested in the various uses of whole blood, blood plasma, and plasma substitutes in emergencies, battle injury, burns, chronic infection and protein depletion due to starvation or disease. Much work is being done on plasma substitutes, but as a rule these substitutes at best can tide the body over an emergency of a day or so to permit the normal production of plasma protein within the body to be resumed. Obviously it is far better for the body to produce its own plasma proteins than to receive them from outside, though plasma proteins introduced parenterally can supply all the protein needs of the body over many weeks.[4] The plasma proteins supply much of the cell protein requirements and are in a constant state of depletion and repletion.[6] The repletion of plasma proteins comes largely from the liver. The body makes its own plasma protein from reserve stores in emergencies or from the incoming diet proteins normally. The body can make plasma proteins and maintain nitrogen balance when the sole source of nitrogen is a protein digest or a mixture of the 10 amino acids[21] essential for growth.

Fortunately for us, this laboratory has been enabled to use pure crystalline amino acids* in various mixtures, parenterally or by mouth, to study plasma protein production and nitrogen balance first in dogs and subsequently in man. This report includes material from various papers recently published—method details, amino acid mixtures and related histories must be consulted in the original papers.

Amino acids (10 of the more than 20 found in natural proteins) were shown by Rose and associates[21] to be required for satisfactory growth in rats. These 10 essential amino acids were: threonine, valine, leucine, isoleucine, lysine, tryptophane, phenylalanine, methionine, histidine and arginine. It was shown later in this laboratory[11,16] that these same amino acids parenterally in dogs as the sole source of nitrogen will cause ample *new plasma protein* production. This is comparable to the response following a similar nitrogen intake of some good natural diet protein.

Intensive study of the amino acids as they are used in the body economy is very much to be desired. Many laboratories will be increasingly occupied with these problems in the near future. We know very little about the influence of single amino acids upon body metabolism but recent work with methionine[7,18] and cystine (Table 1) are intriguing. It is at least possible that variable mixtures of amino acids may have specific effects on body metabolism in health and in diseased states. The possibilities here are too numerous to be discussed but the call for more investigation is obvious. It is our conviction that in these dog experiments (Tables 1 to 3) the various introduced amino acids are largely assembled in the liver to form plasma proteins which may then be used to supply body protein needs, rather than that each cell picks up the amino acids from the blood to make its own specific cell protein.

The production of new plasma protein in dogs is known to be directly related to the kind and quantity of the diet protein

* We are indebted to Merck & Company, Inc., for a generous supply of pure amino acids.

intake.[8] This observation is based upon tests in standardized hypoproteinemic dogs, depleted of circulating plasma protein and reserve protein by bleeding followed by immediate return of red blood cells suspended in saline (plasmapheresis). If the diet protein intake be limited to 1 gm. per kilo body weight, the daily removal by this plasmapheresis procedure of about 20% of the circulating plasma will reduce the plasma protein level from the normal of 6 to 7% to 4% in 1 to 3 weeks. At this hypoproteinemic level plasma protein regeneration is strongly stimulated, but with the low protein intake the daily amount of plasma removal must soon be reduced to about 10% of the total circulating protein. Subsequent variations in the kind and quantity of the protein intake are reflected in the amount of plasma protein which must be removed to maintain a steady hypoproteinemia. Many tests of food proteins and several of amino acid supplementation of food proteins have been previously reviewed.[14]

intake from higher to lower. Also the nitrogen balance was negative. A sharp decline in plasma protein production occurred in Period 19 with zero diet protein intake.

Cystine added in Period 20 boosted the plasma protein production. It was a short-lived stimulation, gone by Period 21, but offers food for speculation regarding internal metabolism. Moreover, it is practical evidence of the possible pitfalls in any conclusions drawn from short-term experiments. It is obvious that *more* than cystine went into the plasma protein produced. If a supposedly complete mixture of amino acids had been given with the cystine, credit might have been given to the mixture rather than to the cystine. A complete mixture except for *cystine* substituting for *methionine* by mouth again stimulated plasma protein output in Period 22. But weight loss occurred and the test could not be continued. A completely adequate source of protein nitrogen

TABLE 1.—AMINO ACIDS IN PLASMA PROTEIN PRODUCTION

Ten Essentials (Va, Vb) Very Effective Orally or by Vein

(Dog 41–187)

Period (7 days)	Diet	Nitrogen intake: Amino acids (gm.)	Nitrogen intake: Basal (gm.)	Urine nitrogen (gm.)	Plasma protein removed (gm.)	Plasma protein level (%)	Weight (kg.)
18	Liver		11.2	15.3	22.2	3.99	10.2
19	Protein-free	..	0.1	10.1	3.7	3.99	9.9
20	Protein-free + cystine	0.8	0.3	5.0	14.1	4.15	9.5
21	Protein-free + cystine	0.8	0.3	4.5	1.8	3.76	9.3
22	Amino acids VI	18.5	0.3	18.7	18.3	4.39	9.0
25	Amino acids Va	18.3	0.3	7.7	15.3	4.27	9.2
26	Amino acids Va	18.3	0.3	9.0	15.3	4.10	9.3
27	Amino acids Vb minus glycine	12.4	0.3	7.9	17.6	4.01	9.0
28	Amino acids Vb minus threonine	18.1	0.3	17.4	8.4	3.90	9.2
29	Amino acids Vb, i.v.	16.7	0.3	17.1	16.3	4.27	9.0
30	Amino acids Vb—VII, i.v.	18.3	0.3	15.5	16.1	4.01	8.4

The 10 essential amino acids were found to be effective in plasma protein production in dogs.[11] Table 1[11] contains portions of the published data from a continuous 30 week study. The plasma protein removed in the 18th week was more than that which could be related to the current liver protein intake of 70 gm. (11.2 gm. nitrogen × 6.25). The immediately preceding weeks afforded a much higher protein intake and this *carry over* in production is expected with any change of protein had not been provided in Period 22. Nitrogen balance was slightly negative.

When the 10 essential amino acids plus glycine were provided by mouth as noted in Periods 25 to 27, Table 1, positive nitrogen balance and plasma protein production were good. Throughout all the tables the mixtures designated by the Roman numeral V contained the 10 essentials plus glycine.[11] The modifying letters indicate variations in proportion or form. For example, Vb was the same as Va

except that the l(−)-leucine in Va was replaced by double the quantity of dl-leucine. The good production of plasma protein in Weeks 25 and 26 continued in Week 27 when the glycine was omitted. Production dropped sharply, however, when *threonine* was omitted.

Given by *vein*, the amino acids including threonine supported a return of plasma protein production, Table 1. But weight declined and nitrogen balance was questionably maintained. The excellent tolerance to the amino acid mixtures prompted further trials by vein.

at the end of the 30 weeks was 11.3 kg. Various slight modifications of the 10 essential amino acid mixtures are indicated in Table 2, second column. Details are given in an earlier article[16] which adds other confirmatory data.

Comparison of utilization of amino acids given by *oral* administration with that of *parenteral* administration is of interest. Such an experiment is presented in Table 3[9] from a recent report. The differences are not large, but it appears definite that the *oral route favors superior utilization for plasma protein formation and for nitrogen*

TABLE 2.—TEN ESSENTIAL AMINO ACIDS IN PLASMA PROTEIN PRODUCTION GIVEN INTRAVENOUSLY, SUBCUTANEOUSLY, OR INTRAPERITONEALLY

(Dog 41-187)

Period (7 days)	Amino acid mixtures	Nitrogen intake: Amino acids (gm.)	Nitrogen intake: Basal (gm.)	Urine nitrogen (gm.)	Plasma protein removed (gm.)	Plasma protein level (%)	Weight (kg.)
4	Vg, i.v.	18.7	0.3	15.4	23.5	4.14	11.9
5	Vg, i.v.	18.7	0.3	14.4	18.1	3.85	11.8
6	Vg, i.v.	18.7	0.3	14.6	14.6	3.90	11.5
7	Vg, s.c.	18.7	0.3	12.0	12.9	3.91	11.8
8	Vj, s.c. (Vg with less glycine)	11.1	0.3	7.2	15.0	3.98	11.7
9	Vj, s.c.	11.1	0.3	6.6	17.0	3.89	11.6
10	Vm, s.c.	12.4	0.3	6.8	11.0	3.82	11.7
11	Vm, i.p.	12.4	0.3	10.2	18.6	4.02	11.3
12	Vo, s.c.	13.3	0.3	8.9	16.3	3.92	11.1

TABLE 3.—TEN ESSENTIAL AMINO ACIDS IN PLASMA PROTEIN PRODUCTION—ORAL AND PARENTERAL ADMINISTRATIONS COMPARED

(Dog 42-1081)

Period (7 days)	Amino acid mixture	Nitrogen intake: Amino acids (gm.)	Nitrogen intake: Basal (gm.)	Urine nitrogen (gm.)	Plasma protein removed (gm.)	Plasma protein level (%)	Weight (kg.)
13	Casein		21.2	13.0	19.4	4.33	8.8
14	Vah, s.c.	18.0	3.6	20.6	13.9	4.03	9.1
15	Vah, s.c.	18.0	3.6	14.4	13.2	4.15	9.1
16	Vah, oral	18.0	3.6	12.3	15.2	4.14	9.0
17	Vah, oral	18.0	3.6	12.1	24.7	4.30	9.0
18	Vah, i.v.	18.0	3.6	17.0	14.9	4.19	8.9
19	Vah, i.v.	18.0	3.6	18.0	15.8	4.11	8.9
20	Vah, s.c.	18.0	3.6	15.1	17.9	4.12	9.3
21	Vah, s.c.	18.0	3.6	16.2	14.7	4.10	9.4

The ease of use and effectiveness of *amino acids given parenterally* were convincingly shown in the observations of Table 2,[16] part of a continuous 30 week period of parenteral nitrogen administration. There was no question here of maintenance of positive nitrogen balance. Injections by vein, subcutaneously, and into the peritoneal cavity were all well tolerated and well conserved for nitrogen needs, including ample production of plasma protein. The slight weight loss in these earlier periods was corrected later when larger intakes were given and the weight

balance. Other observations such as those in Table 1 and those in man as presented below confirm this difference.

The better conservation of nitrogen after oral intake is usually more definite than the difference in plasma protein production. This conservation is reflected chiefly in the urinary constituents other than urea and ammonia. The difference is also obtained when protein digests are compared orally and parenterally.[10,13,17] Escape of amino acids into the urine no doubt is part of the explanation but other factors are probably involved. Whereas

we have found that the total undetermined urinary fractions (*i. e.*, non-urea-and-ammonia) are similar for comparable injections of amino acid mixtures and protein digests, others[1] have noted that urinary amino acids are lower after injection of protein digests. It would appear that other fractions of the undetermined nitrogen group increase more after digest injection than after amino acid injection to account for the equality of the totals. It is fair to say that different protein digests vary in composition and different findings from various laboratories may reflect some of these differences.

The good utilization of synthetic mixtures made up largely of *synthetic amino acids* is somewhat surprising. Undoubtedly some of the urinary nitrogen after parenteral injection of mixtures containing 6 or 7 amino acids, half of which consist of the optical forms not found in natural proteins, contains *some of these unnatural isomers*. It is believed that in rats the first 5 of the 10 essentials as listed above are utilizable upon oral intake only in their natural forms.[21] In the rat some d(+)-leucine may be converted to the natural form[19] but apparently most of unnatural lysine is excreted as such.[20] In mice[24] and in man[1,22] unnatural tryptophane appears *not* to substitute upon oral intake for the natural form and to be associated with the appearance of an uncommon indole derivative in the urine. Moreover, in man feeding of racemic phenylalanine is followed by greater loss of phenylalanine into the urine than is noted after ingestion of the natural form.[1]

This information about unnatural isomers is of biochemical interest and some physiologic importance but does not justify conclusions as to *toxicity*. No demonstration of real toxicity to unnatural or natural amino acids in the mixtures, the concentrations, and the quantities used in our observations has been found. Certain transient intolerances have been studied. The subject of *tolerance* to amino acid mixtures is important. *Tolerance* and *toxicity* overlap and are difficult to define. We recognize that almost any substance in high enough quantity may be poisonous. But because an artificial diet containing 10% methionine may be injurious[5] it is not to be concluded that the 3% methionine in milk protein is 30% as injurious! In studying tolerances to the intravenous injection of amino acid mixtures and protein digests we have been concerned with *transient disturbances*, chiefly nausea and vomiting.

No evidence of serious or persistent injury has ever been noted after any of hundreds of injections into animals and man using the materials here studied. A recent report on *tolerance* to amino acid injection emphasizes the low tolerance to mixtures containing *glutamic acid*.[15] *Aspartic acid* is likewise prone to stimulate vomiting.[9,15] Proper mixtures of the 10 essential amino acids are much better tolerated than any protein digests which contain high contents of glutamic acid, such as casein digests. Some data have been presented indicating improved tolerance to the 10 essentials by the addition of glycine.[15] In certain quantities alanine, serine, proline, and hydroxyproline were also found to be well tolerated in the mixtures.

A mixture which could be injected into dogs at rates greater than 10 mg. nitrogen per kilo per minute in quantities greater than 300 mg. nitrogen per kilo consisted of dl-threonine 7, dl-valine 15, l(−)-leucine 10.9, dl-isoleucine 9.9, l(+)-lysine-.HCl.H_2O 10.9, dl-tryptophane 3, dl-phenylalanine 9.9, dl-methionine 6, l(+)-histidine.HCl.H_2O 5, l(+)-arginine.HCl 5, glycine 9.9, dl-a-alanine 4, dl-serine 2, l(−)-cystine 0.5, and l(−)-tyrosine 1 (all given in %). This exact mixture has not been tested in man.

Solutions of crystalline amino acids can be injected subcutaneously in relatively high concentration without disturbance. In dogs and man[10] more than 10% solutions in distilled water are well tolerated. In premature infants absorption of such concentrated solution is slow and a more dilute solution is to be preferred.

The first data in man on the prolonged

use of crystalline amino acids for parenteral feeding are summarized in Table 4.[2] The mixtures used consisted of the 10 essentials plus glycine and were given intravenously and subcutaneously. The caloric intake during the first 5 days was less than 800 calories per day and nitrogen balance was not obtained until Periods 2 and 3 when the caloric total daily was above 1200. A modest nitrogen intake needs a certain caloric protection by carbohydrate. It would be an interesting experiment to test whether or not nitrogen balance might be obtained from a sufficiently high intake of pure amino acids in the total absence of carbohydrate and fat. In the observations of Table 4, Periods 5 to 7, when the caloric intake was an ample 2000 to 3300 calories daily, nitrogen balance was strongly positive and weight gain considerable. With return to a diet of natural protein in Periods 8 and 9, total nitrogen retention became greater, largely by the reduction in the undetermined urinary nitrogen fraction. Explanation of this change has been discussed above. The patient made a surprising recovery based upon successful surgery made possible largely by preoperative parenteral feeding.

Amino acids parenterally were virtually the sole source of nitrogen in Period 1 from a recent report reproduced in Table 5.[10] With the high intake, balance was positive—evidence that the 10 essential amino acids plus glycine given parenterally are alone adequate for the nitrogen requirements of man. This patient, J. S., 21 years, was severely depleted of body protein. Nitrogen balance was continued during parenteral injections during Periods 2 and 3, but was impossible due to poor food intake and vomiting when oral feeding was attempted in Period 4. Recovery

TABLE 4.—TEN ESSENTIAL AMINO ACIDS PARENTERALLY IN MAN—POSITIVE NITROGEN BALANCE AND WEIGHT GAIN

F. K., age 63; pyloric ulcer with obstruction.

		Nitrogen intake		Nitrogen output					
Period (5 days)	Amino acids	Amino acids (gm.)	Basal (gm.)	Urine total (gm.)	Urine urea-NH_3 (%)	Urine undetermined (gm.)	Feces (gm.)	Nitrogen balance* (gm.)	Weight (kg.)
1	Vh, i.v., s.c.	73.5	0.5	86.5	78	19.7	0.9	−15.8	44.1
2	Vh, i.v., s.c.	88.3	5.4	88.1	72	24.8	0.9	+ 3.7	46.0
3	Vn, i.v., s.c.	73.1	7.2	76.9	72	21.8	0.9	+ 1.6	44.2
4	...	..	27.2	33.3	84	5.2	1.9	−10.7	43.5
Interval of 21 days, with subtotal gastrectomy on 9th day.									
5	Vn, i.v., s.c.	72.9	13.7	68.0	71	19.3	7.4	+11.2	41.6
6	Vx, i.v., s.c.	64.4	17.4	53.9	67	17.9	7.3	+20.6	43.3
7	Vx, i.v., s.c.	65.5	16.7	59.4	66	20.0	7.7	+15.1	43.9
8	...	..	80.0	44.3	83	7.6	7.5	+28.2	45.9
9	...	..	80.0	42.9	84	7.0	8.5	+28.6	47.0

* Nitrogen of vomitus and Wangensteen drainage deducted.

TABLE 5.—TEN ESSENTIAL AMINO ACIDS PARENTERALLY YIELD NITROGEN BALANCE AS SOLE SOURCE OF NITROGEN

J. S., age 21, chronic ileitis with obstruction.

		Nitrogen intake		Nitrogen output					
Period (5 days)	Amino acids	Amino acids (gm.)	Basal (gm.)	Urine total (gm.)	Urine urea-NH_3 (%)	Urine undetermined (gm.)	Feces (gm.)	Nitrogen balance* (gm.)	Weight (kg.)
1	Vu, i.v., s.c.	130.0	0.6	108.4	57	46.1	11.2	+ 8.4	38.9
2	Vu, i.v., s.c.	65.2	3.4	64.7	60	25.8	5.8	− 1.9	
3	Vu, i.v.	65.3	8.3	54.0	57	22.9	11.8	+ 6.6	38.6
4	(Operation)	0	16.5+	22.1	76	5.4	..	..	37.1
5	Vu, i.v.	91.7	2.2	82.1	61	31.9	6.0	+ 5.8	
6	None	0	78.3	31.6	79	6.6	10.3	+36.4	37.2
H. S., age 55, carcinoma of head of pancreas.									
1	Vua, i.v., s.c.	59.2	0.2	68.4	76	16.5	4.7	−14.8	60.4
2	Vub, s.c.	58.3	0.0	52.3	68	16.7	6.3	− 1.8	

* Nitrogen of vomitus and Wangensteen drainage deducted.

from resection of a segment of ileum at the end of Period 4 was uneventful. Nitrogen balance was continuous in Period 5. Better utilization of natural food protein by mouth is again demonstrated in Period 6.

Patient H. S., 55 years, the second patient in Table 5, received the amino acid solution almost entirely *subcutaneously*, partly because suitable veins were difficult to find. Nitrogen balance was total weight gain was 10 kilos and the clinical improvement in the ulcerative colitis was marked. Abdominal distress and diarrhea disappeared although the colon lesions remained. Reduction in fecal nitrogen was considerable from the high level of Period 1.

Tolerance to the mixture Vuj was only moderately better in this patient of Table 6 than to Amigen. There was nausea and vomiting with too rapid injections of vari-

TABLE 6.—TEN ESSENTIAL AMINO ACIDS PARENTERALLY LONG CONTINUED—WITH NITROGEN BALANCE AND WEIGHT GAIN

M. E., age 26, chronic ulcerative colitis.

		Nitrogen intake		Nitrogen output					
Period (5 days)	Amino acids	Food (gm.)	Amino acids (gm.)	Urine total (gm.)	Urine urea-NH_3 (%)	Urine undetermined (gm.)	Feces (gm.)	Nitrogen balance (gm.)	Weight (kg.)
0	....	..	..	..	..	..	..	..	52.26
1	None	101.5	..	49.5	81	9.3	39.7	+12.3	52.09
2	Varies, i.v.	6.5	68.0	68.3	72	18.9	26.5	−20.3	50.23
3	Amigen, i.v.	15.2	62.6	56.6	67	18.9	12.5	+ 8.7	53.63
4	Vuj, i.v.	15.2	59.9	55.7	69	17.4	14.7	+ 4.7	54.12
5	Vuj, i.v., s.c.	7.5	102.0	93.4	73	25.5	18.7	− 2.6	52.18
6	Vuj, i.v., s.c.	13.9	85.6	82.4	69	25.3	13.6	+ 3.5	54.43
7	Vuj, i.v.	12.0	84.0	80.9	70	24.0	9.1	+ 6.0	53.43
8	Vuk, i.v.	7.4	85.9	76.2	68	24.5	13.9	+ 3.1	54.63
9	Vuk, i.v.	6.9	43.1	44.3	61	17.3	13.7	− 8.0	55.91
10	Vuj, i.v.	6.9	43.1	37.0	60	14.9	13.8	− 0.8	57.19
11	Vuj, s.c.	6.9	43.2	36.4	65	12.8	13.2	+ 0.5	58.19
12	Vuk, oral	6.9	43.3	25.1	49	12.7	17.0	+ 8.1	58.28
13	Vuk, oral	6.9	43.3	27.7	49	14.1	16.1	+ 6.4	59.09
14	Vuk, oral	6.9	43.3	27.4	48	14.2	13.8	+ 9.0	59.83
15	Vuk, i.v.	6.9	43.3	38.2	63	14.2	lost	..	60.08
16	Vuk minus histidine, i.v.	6.9	40.7	37.8	63	13.9	15.0	− 5.2	60.78
17	Vuk minus histidine, i.v.	6.9	40.7	41.0	66	14.0	11.7	− 5.1	61.27
18	Vuk, i.v.	6.9	43.1	36.2	61	14.2	12.0	+ 1.8	62.13
19	None	101.5	..	61.7	85	9.1	7.5	+32.3	62.50
20	None	101.5	..	65.0	87	8.3	11.5	+25.0	63.21

TABLE 7.—TEN ESSENTIAL AMINO ACIDS BY MOUTH COMPARED WITH AMIGEN AND EGG

M. E., age 26, chronic ulcerative colitis.

		Nitrogen intake		Nitrogen output					
Period (10 days)	Diet	Amino acids (gm.)	Basal (gm.)	Urine total (gm.)	Urine urea-NH_3 (%)	Urine undetermined (gm.)	Feces (gm.)	Nitrogen balance (gm.)	Weight (kg.)
1	Vuj	85.6	5.0	81.3	72	22.5	37.9	−28.5	58.6
2	Vuj	86.6	5.0	52.3	65	18.6	35.7	+ 2.6	59.3
3	Vuj	86.6	5.0	54.2	64	19.6	35.3	+ 2.1	59.5
4	Amigen	90.0	5.0	47.7	75	12.0	41.3	+ 6.0	59.8
5	Amigen	126.0	5.0	62.9	78	14.1	65.0	+ 3.1	59.5
6	Egg	..	87.9	40.6	73	11.1	57.6	−10.3	58.6

not approached until the second period when the caloric intake improved. The patient recovered temporarily to die a year later of the malignant disease.

The observations of Table 6[10] comprise an almost perfect human metabolism study previously reported in detail. For 85 days, Periods 2 to 18, amino acids afforded the chief nitrogen intake except for 5 days with Amigen. During 70 of the 85 days the nitrogen was given parenterally. The ous mixtures in Period 2. This mixture Vuj appears not so well tolerated[12] as some others studied.[15] The utilization of Amigen and Vuj in Periods 3 and 4 respectively was quite comparable. The similar quantities of undetermined nitrogen for these 2 periods should be noted in view of the discussion above. The undetermined nitrogen was much less when natural protein was given in Periods 1, 19 and 20. It did not decline significantly when

the amino acids were given orally in Periods 12 to 14 but the urea and ammonia fraction dropped sharply. Nitrogen balance became strongly positive.

Histidine omission in Periods 16 and 17, Table 6, caused a rise in urinary nitrogen and negative balance. It appears that histidine may be required by this patient with chronic ulcerative colitis. Both histidine and arginine may apparently be omitted from the intake of normal man in nitrogen equilibrium.[23]

Orally the amino acid mixture and Amigen were rather similarly utilized *in toto* although the proportions were different in the data of Table 7.[10] This same patient as studied in Table 6 did not obtain the same clinical improvement from the oral administration of both the amino acids and the basal diet as he did from the parenteral feeding of Table 6. The amino acids were more palatable and associated with a lower fecal nitrogen than the Amigen, but the urinary total nitrogen and the undetermined fraction were higher. When whole egg replaced the Amigen the urine nitrogen fractions dropped conspicuously.

Discussion. The above observations and comment concern the use of complete mixtures of amino acids for general nutrition. Single or several amino acids in groups may find a practical place in the supplementation of diet protein. Other more specific uses may be discovered. As a single amino acid, *methionine* has already found a place in clinical therapy[3] following demonstration experimentally of its detoxifying action.[7,18]

Synthetic amino acid mixtures permit obvious flexibility not possible with protein digests. It is not unreasonable to suspect that injury of a specific tissue might be most rapidly repaired by a mixture of amino acids corresponding to that tissue. We believe, however, that most tissue proteins are constructed from plasma proteins by more or less modification of plasma protein molecules, sometimes probably with addition or subtraction of amino acids. If this be true then the amino acid constituents of these plasma proteins might dictate the basic make-up of the amino acid mixture to be given the patient. If, for example, one would enhance the production of protective globulins a knowledge of the make-up of the gamma globulins might determine the best admixture of amino acids for that specific purpose. For other specific purposes, other admixtures might be indicated and would be permitted by use of synthetic mixtures.

The amino acid mixtures are better tolerated parenterally and more palatable orally than various protein digests tested in this laboratory. On the other hand the practical problems and the economics of large scale production of pure amino acids will have much to do with determining the extent of use of such materials.

The importance of adequate protein nutrition for all patients appears obvious to most of us, but too often obvious needs are neglected. As a single item in the treatment of all patients we believe that adequate protein nutrition cannot be surpassed in importance. Some day physicians should have within easy reach the necessary materials for maintaining protein nutrition in the sick or injured patient where effective parenteral administration is a necessity—a prospect for the near future.

Summary. Amino acids can supply the protein nitrogen requirements of the body. The so-called 10 essential amino acids in suitable amounts can be given by mouth, by vein, subcutaneously or intraperitoneally with equal success in maintaining nitrogen and weight equilibrium.

These 10 essential amino acids are threonine, valine, leucine, isoleucine, lysine, tryptophane, phenylalanine, methionine, histidine and arginine. Glycine is usually added to this mixture.

By mouth the amino acids are utilized a little more completely than when given parenterally. Our experiments give no evidence that the unnatural isomers of the amino acids are toxic and some are probably used in the body.

These amino acid mixtures can be given

rapidly in 10% solution parenterally and cause less clinical disturbance than any protein digests so far tested. Glutamic acid in digests or amino acid mixtures is not well tolerated by vein and may induce vomiting.

Abundant production of plasma proteins in standardized dogs is readily demonstrated as due to these amino acids as the sole source of nitrogen. The production of new plasma protein due to amino acids in general corresponds favorably with the response to high grade diet protein in equivalent amounts.

Our first observations were upon dogs but subsequent observations on human patients gave the same picture.

These amino acid mixtures are well utilized by patients suffering from chronic infection (colitis), gastro-intestinal disturbances (partial obstruction) or cancer cachexia.

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THE EFFECT OF SALICYLATE THERAPY ON THE WELTMANN SERUM COAGULATION REACTION AND ITS USE AS A PROGNOSTIC TEST IN RHEUMATIC FEVER*

By D. E. Ward, Jr., M.D.
AND
George T. Harrell, M.D.
WINSTON-SALEM, N. C.
(From the Department of Medicine, Bowman Gray School of Medicine of Wake Forest College, and the North Carolina Baptist Hospital)

An objective laboratory test which can measure the activity of a disease process and aid in the evaluation of prognosis is constantly being sought. For a long time the clinical course of the patient with an infectious disease has been compared with the temperature, and total and differential white blood cell counts; more recently serial determinations of the sedimentation rate of erythrocytes have been widely used. Weltman's discovery that serum is coagulated by solutions of calcium chloride has provided another useful test.[9]

Chemotherapeutic agents alter the clinical course of infectious diseases by controlling growth of the etiologic agent or by abolishing symptoms of the disease. In the latter case a false sense of security regarding the arrest of the pathologic process may arise. The introduction by Coburn of massive salicylate therapy for controlling the clinical manifestations of rheumatic fever and suppressing the inflammatory process has created the need for a prognostic laboratory test which is unaltered by salicylates.[2] The rationale of salicylate therapy in relation to antigen-antibody reactions and hypersensitivity in rheumatic fever has recently been reviewed by Aikawa.[1] The sedimentation rate has been the most widely used laboratory aid for the determination of rheumatic activity but it has been shown to be altered *in vitro* by the presence of salicylates.[5] Concentrations necessary to depress the sedimentation rate can be achieved *in vivo* by massive salicylate therapy.

The Weltmann reaction has been shown to be equal or superior to the sedimentation rate as a prognostic aid in rheumatic fever.[7] Since the sedimentation rate is affected by salicylate therapy, the Weltmann reaction, if it is not affected by salicylates, should be a superior test. The effect of salicylates on the Weltmann reaction was studied *in vitro*. After alteration in the coagulation band was found only with high concentrations of salicylates, the Weltmann coagulation reaction in the presence of various blood levels of salicylate was compared *in vivo* with the sedimentation rate, and the total white blood cell count.

Material and Methods. *In vitro studies:* Sodium salicylate was dissolved in normal human serum to make a 1% solution. Weltmann coagulation bands were determined on samples of serum from 4 normal individuals. Aliquots of these samples were diluted with the stock salicylated serum, so that the final concentrations were 200, 400, 600, 800, 1000, 2000 and 6000 γ per cc. of serum. These levels approximate those found in the blood of patients receiving salicylate therapy.

In vivo studies: Over a period of 6 months, 86 Weltmann coagulation tests were done on 26 rheumatic patients on the wards or in the Out-Patient Clinic of the North Carolina Baptist Hospital. The clinical diagnoses in this group are shown in Table 1.

The total white blood cell counts, sedimentation rates, and blood salicylate levels of these patients were also followed, but only those determinations done on the same day as the Weltmann test are considered in the analysis of data.

* Presented at the meeting of the Southern Section of the American Federation for Clinical Research, Atlanta, Georgia, December 8, 1945.

Weltmann reaction: A stock solution of 10% calcium chloride hexahydrate ($CaCl_2.6H_2O$) was prepared; this compound was used, as has been suggested by Schweinburg and Evans, in order to keep the pH in the favorable range of 7.2 to 7.8.[8] From the 10% solution 10 stock dilutions were made, containing in arithmetic progression 0.1 to 0.01% calcium chloride. The tests were run by shaking 5 cc. of each calcium chloride dilution with 0.1 cc. of non-hemolyzed serum in small test tubes arranged in a rack. The rack was left in a boiling water bath for 15 minutes and the reaction was then read. On each series of tests two control tests with normal serum were run simultaneously; the coagulation bands on the normal sera were always 6.

Figure 1 is a scatter chart of the results. The salicylate levels varied from 0 to 1073 γ per cc.; the coagulation band usually fell below 6, since rheumatic diseases in the acute stage are characterized by inflammation. An analysis of co-variation of these data (Table 2) failed to reveal any significant degree of correlation between the two determinations, either between the means of tests on the 27 patients or within series of tests on the same patient. Both of these correlations are statistically non-significant and may therefore be attributed to chance variations.*

Weltmann tests were done on additional hospitalized patients who were receiving salicylate therapy for various conditions unrelated to the rheumatic state. The data are not included in this report, but the results closely parallel those in the rheumatic group.

TABLE 1.—DISTRIBUTION OF CASES

Clinical Diagnosis	Number of cases
Rheumatic fever:	
Active rheumatic fever without demonstrable heart disease	8
Active rheumatic fever with heart disease	3
Rheumatic chorea without demonstrable heart disease	2
Inactive rheumatic heart disease, bacterial endocarditis	1
—	14
Atrophic arthritis	10
Erythema nodosum	1
Hypertrophic arthritis	1
Total	26

Sedimentation rate: Five cc. of venous blood was collected in specially prepared bottles containing 4 mg. of potassium and 6 mg. of ammonium oxalate. The oxalated blood was placed in Wintrobe tubes and the observed values were corrected according to the method of Wintrobe and Landsberg.[10]

Blood and salicylate levels: Salicylate levels were determined on fasting venous blood according to the method of Coburn.[2]

Results. *In vitro studies:* The coagulation band was found to be unchanged by the addition of 200 to 800 γ of sodium salicylate per cc. The addition of 1000 to 6000 γ per cc. increased the coagulation band from 6 to 7; such levels would rarely be achieved in patients and would be accompanied by symptoms of salicylism.

In vivo studies: Blood salicylate levels: A total of 86 determinations of the blood salicylate levels were made on the same day that the Weltmann test was done.

Sedimentation rate: Sixty Weltmann tests were done on the same day that the sedimentation rate was determined. Figure 2 is a scatter chart of the results. The mean line has a negative slope, indicating that in general the higher the sedimentation rate, the lower the coagulation band will be. As the sedimentation rate decreases toward normal, the coagulation band approaches a normal value of 6.

White blood cell count: In 19 cases 44 Weltmann reactions were determined on the same day that a white blood cell count was made. Figure 3 shows a scatter chart of these data. The mean line has a negative slope, indicating that in general the

* A statistical analysis of these two sets of data was made by Dr. Charles W. Cotterman.

TABLE 2.—ANALYSIS OF CO-VARIATION OF BLOOD SALICYLATE LEVEL AND WELTMANN REACTION

Source of co-variation	Degrees of freedom	Correlation coefficient
Between means of patients	25	−0.131 (non-significant)
Within patients	56	+0.070 (non-significant)
Total	84	−0.026 (non-significant)

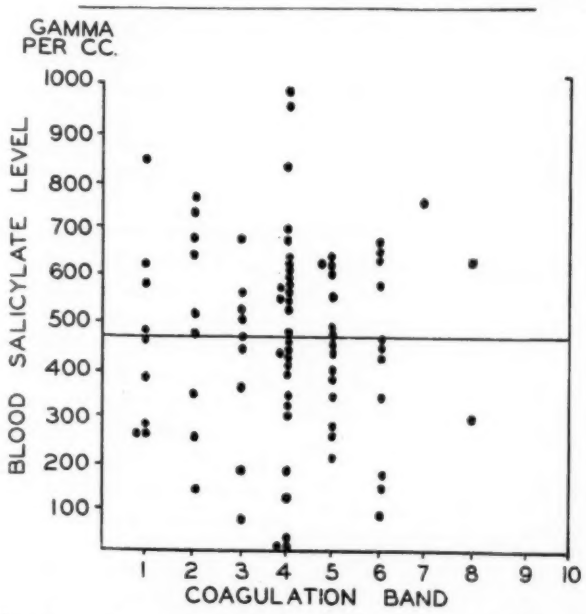

FIG. 1.—Weltmann reaction compared with blood salicylate level in 26 rheumatic patients.

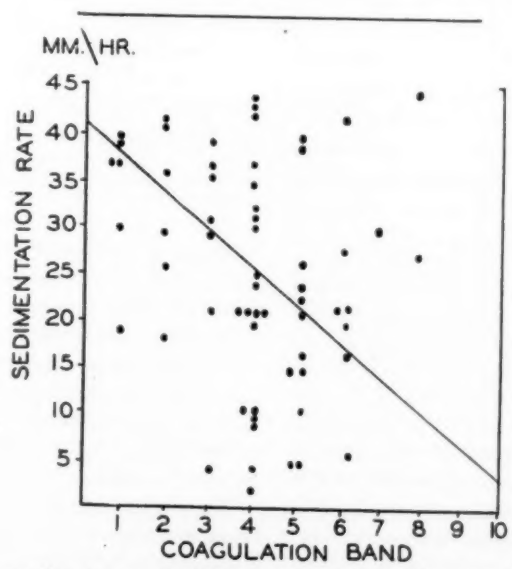

FIG. 2.—Weltmann reaction compared with corrected sedimentation rate in 22 rheumatic patients receiving salicylates.

higher the white blood cell count, the lower the coagulation band will be.

Discussion. *Weltmann reaction as a prognostic aid in rheumatic fever:* The factor of greatest importance in determining the prognosis of rheumatic fever is the presence or absence of active inflammation, with damage to the heart. In exudative reactions, which are associated with acute infection, the coagulation band is usually shifted to the left. This shift is paralleled by an elevation of the sedimentation rate and white blood cell count.[7] If the myocardium is involved in the inflammatory or exudative process, the electrocardiogram may show an alteration of the PR interval and complexes; this test gives no information on the state of the valves.

The development of fibrosis is accompanied by a shift to the right in the coagulation band and is part of the healing process which may cause distortion of the heart valves by excessive scarring. The detection of this process before the development of audible murmurs would be of great aid in determining the amount of activity the patient should be allowed. Comparisons of the Weltmann reaction and the sedimentation rate in rheumatic fever and other processes—such as tuberculosis—which show similar progression from exudation to fibrosis have shown that the coagulation band does not always correspond to the sedimentation rate, but appears to reflect more accurately the anatomic pathologic change.[4]

Comparison of the Weltmann reaction and the sedimentation rate in the presence of salicylates: The relationship between the Weltmann reaction and the corrected sedimentation rate in patients with rheumatic fever has been shown by other investigators to be roughly parallel.[7] These studies were done before the introduction of massive salicylate therapy by Coburn, and it is not clear whether any salicylates were administered to the patients during these previous studies.

The mechanism of the Weltmann coagulation reaction is not well understood. It is thought to be a physico-chemical change in the state of the serum proteins initiated

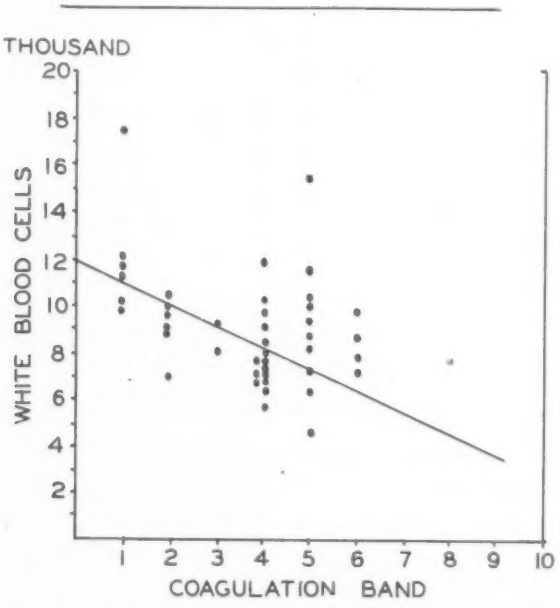

FIG. 3.—Weltmann reaction compared with white blood cells in 19 rheumatic patients receiving salicylates.

by the addition of calcium ions. It should be noted that the Weltmann test is performed with serum and the sedimentation rate determination with plasma; no extraneous ions are introduced in the collection of specimens for the Weltmann reaction. The sedimentation rate has been found to parallel closely the level of plasma fibrinogen, a substance thought to be formed in the liver;[3] the chemical relationship of salicylates to dicumarol has recently been pointed out, and dicumarol has been shown to depress plasma prothrombin by the effect on the liver.[6] Hence, the sedimentation rate may be artificially altered by the effect of salicylates on the production of fibrinogen as well as by the effect on the disease process.

Lichty and Hooker conclude that a salicyl compound administered to patients as acetylsalicylic acid may have the ability to lower the sedimentation rate artificially.[5] They quote studies of Bendien, Newberg and Snapper, who noted that when sodium salicylate is added to human blood *in vitro*, the erythrocyte sedimentation rate is greatly reduced. Preliminary experiments of the former authors indicated that the minimal concentration of sodium salicylate necessary to depress the sedimentation rate *in vitro* was 90 to 120 mg. per 100 cc. (900 to 1200 γ per cc.*); our *in vitro* studies indicate the Weltmann reaction is altered only slightly at this range. In patients the marked drop in the sedimentation rate noted after the institution of acetyl salicylic acid therapy in ordinary doses is reversed by withdrawal of the drug. The variation in the sedimentation rate is far greater in proportion than is that in the Weltmann coagulation band noted in the present report. Both the *in vitro* and the *in vivo* data seem to indicate that the Weltmann reaction is relatively less altered by even high levels of salicylate than is the sedimentation rate. Hence, it should be superior as a prognostic aid.

Comparison of the Weltmann reaction and the white blood cell count: The white blood cell count has been used as a measure of tissue destruction in non-infectious processes—such as myocardial infarction—as well as in infectious processes. The data in Figure 3 indicate that there is a rough parallel between the white blood cell count and the coagulation band. It has been shown that extraneous factors, such as the time of day and the relation to meals, have a marked effect on the white blood cell count. These factors do not alter the Weltmann coagulation band.

Summary. 1. Serial studies of the Weltmann coagulation reaction, the corrected sedimentation rate, and the white blood cell count were made over a period of 6 months in 26 patients with rheumatic states who were receiving salicylate therapy.

2. The Weltmann coagulation reaction was found to be unaltered *in vitro* or *in vivo* by levels of salicylates commonly attained in the blood.

3. Even in the presence of salicylate therapy a low Weltmann coagulation band, an elevated sedimentation rate, and an elevated white blood cell count are all indications of an inflammatory process. The coagulation band is least affected by extraneous factors, however, and gives the most uniform results.

4. The Weltmann coagulation band agreed more closely with the clinical course and symptoms in patients studied than did the sedimentation rate or white blood cell count.

5. The Weltmann coagulation reaction seems to be a better measure of activity and a more accurate index to the prognosis of rheumatic fever in patients receiving salicylate therapy than other laboratory aids now available.

* Since the paper was submitted for publication, Homburger has published in this Journal (AM. J. MED. SCI., **210**, 168, 1945) *in vitro* studies which clearly show depression of the sedimentation rate by concentrations of as little as 30 mg. of sodium salicylate per 100 cc. of plasma, if the plasma is allowed to stand for 24 hours before the test is run.

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PSITTACOSIS TREATED WITH SULFONAMIDE DRUGS

By John A. Toomey, M.D.
and
Ralph C. Lohrey, M.D.
Cleveland, Ohio

(From the Department of Contagious Diseases, City Hospital, and the Department of Pediatrics, Western Reserve University)

Five patients ill with psittacosis were admitted to the Department of Contagious Diseases, Cleveland City Hospital during January 1942. Two others exposed to infected parrakeets in the same pet shop were admitted to another hospital; one of these died. The ages of the patients in City Hospital were 34, 36, 37, 44 and 71 years; 2 were females and 3 were males.

The most common symptoms were extreme malaise, weakness, chills and fever. Others were headache, constipation, myalgia and a cough which in 2 patients was dry, irritative and essentially non-productive.

Roentgen examination of the lungs showed pneumonia to be present in all patients, the character of which was consistent with the diagnosis of psittacosis bronchopneumonia. It cleared on an average of 19.4 days, the least number of days being 15 and the greatest 25.

In Patients 1 and 4 (Table 1) there was a drop in the temperature curves after sulfonamide drugs had been administered. Clinically, however, they remained extremely ill, having general malaise and weakness for a long time. Neither was benefited. Patient 5 was not very ill and his constitutional symptoms disappeared soon after admission. Neither sulfapyridine nor sulfathiazole brought down his temperature.

Patients 2 and 3 were seriously ill on admission and sulfapyridine had no effect on the clinical course; if anything the patients seemed worse. The extreme malaise in these 2 patients was still present on the 27th and 31st hospital days, respectively, the days when they were discharged from the hospital.

Patient 3 was probably the most acutely ill of all the patients. She was a typical case, a direct exposure, and yet she did not have a positive complement-fixation test nor did she respond to sulfonamide drugs.

In Patient 4 the temperature became normal within 24 hours after admission, but it took almost 2 weeks before the lungs became clear.

Of the 5 patients treated with sulfonamide drugs, Patient 1 was the only one that might have been said to have responded somewhat to a sulfonamide in that the temperature became normal within 2 days after treatment started. On the other hand, the patient still had pathologic findings in the lungs which did not clear until approximately the 20th hospital day. It may be that some of the other sulfonamide drugs might have given other results, but certainly it can be said that neither sulfapyridine nor sulfathiazole was the drug of choice in treating this infection. This is the experience of others. Heilman *et al.* advised penicillin in large doses in the comparable disease of ornithosis.[1] Our own clinical guess is that even penicillin would be of little value.

The owner of the store (M. K.) who housed the infected parrakeets, was admitted to another hospital and died from the disease. The blood serum of his wife who had not been hospitalized fixed antigen in a dilution of 1:32 (4+). The complement-fixation test is reliable. However, one has to differentiate psittacosis from lymphogranuloma venereum, since the blood serums of patients ill with the latter disease also react to psittacosis antigens.[2] There was no evidence of this disease in our patients.

Parrakeets were collected from the

TABLE 1.—CLINICAL DATA ON 5 PSITTACOSIS CASES

	1 F. W. No. 239951	2 G. F No. 239953	3 N. B. No. 239935	4 I, K. No. 240063	5 M. G. No. 240183
Age	36	37	34	44	71
Sex	M	F	F	M	M
Color	W	W	W	W	W
History of contact	Worked in store, and tended cage	Worked in store, and handled birds	Worked in store, and handled birds	Helped in pet shop where sick parrot died; bitten by parrakeet	Was given pair of love birds
Symptoms on admission	Weakness, malaise, myalgia, chills, headache, fever	Weakness, malaise, fever, constipation, nausea and vomiting, anorexia, cough	Weakness, myalgia, fever, constipation, cough	Weakness, malaise, chills, fever, cough, constipation	Fever, drowsiness, chills and headache
No. days ill before admission	7	8	5	9	3
Chest film on admission	Pneumonia in lower half of left lung field	Pneumonia in lower portion of left lower lobe	Pneumonia in lower half of right lung field	Pneumonia in middle third of left lung field extending toward apex	Negative on admission
Subsequent Roentgen ray examination of chest	11 days later almost complete clearing 17 days later nearly clear; clear on 20th hospital day (H.D.)	14 days later slight clearing Lungs clear 22 days later	14 days later clear	7 days later almost clear 13 days later clear	Pneumonia in right apex and subapical area 8 days later Almost clear 20 days later
Hospital course	Sulfapyridine, total of 21 gm. for 6 days Temp. 39°-39.7° C.; normal in 2 days; discharged on 22nd H.D.	Sulfapyridine, total of 16 gm. for 4 days; sulfathiazole, total of 30.5 gm. from 8th to 12th H.D. Temp. 38° C.; on sulfapyridine it rose to 39° C.; sulfathiazole 8th H.D.; temp. normal on 13th H.D.; vomited, malaise; marked cough present on discharge	Sulfapyridine, total of 27 gm. for 8 days; sulfathiazole, total of 31 gm. from 8th to 13th H.D. Cough for approximately 19 days; temp. 38°-40.8° C.; av. 39° C. for 13 days; normal on 14th H.D.; marked malaise	Sulfapyridine, total of 29.5 gm. for 5 days Temp. on admission 39.5° C.; normal in 24 hrs. and thereafter; in spite of normal temp., patient had malaise up until 6th H.D.	Sulfapyridine, total of 19.5 gm. for 4 days; sulfathiazole, total of 7 gm. from 5th to 7th H.D. Symptoms cleared soon after admission; hiccoughs 9th to 13th H.D.; temp. 38.7° C. on admission; went up to 40° C. on 2nd H.D.; av. 39° C. for 6 days; 38° C. 7th and 8th days; normal thereafter
Blood culture	Negative	Negative	Negative	Not done	Not done
White blood count	5.7	9.6	5.7	8.5	12.0
	52% polymorphonuclears	69% polymorphonuclears	80% polymorphonuclears	55% polymorphonuclears	69% polymorphonuclears
Complement fixation	1/128—4+	1/64—4+	(−)	Bottle broke	Not done

wholesale dealer who supplied birds to the storekeeper previously mentioned as well as to Patient 5 (M. G., the owner of 2 parrakeets). Eleven birds with different code numbers were sacrificed and sent to Dr. Karl F. Meyer of the George Williams Hooper Foundation. Psittacosis virus was recovered from 6 birds. Harlin L. Wynns, Chief of Bureau of Epidemiology of California commented as follows:

"Since six different code numbers were positive, we cannot help but believe that these birds were infected on the premises of the dealer, and we are rather discouraged because of all the states raising and selling shell parrakeets in interstate traffic, we are the only one doing routine systematic testing and permit shipment only of stock tested and found free of infection.

"The shell parrakeet is found infected in its native habitats. Therefore, it is safe to assume that the original importations of such birds into the United States contained infected stock. Furthermore, it is highly improbable that birds raised in states other than California are free of infection.

"We test our stock regularly and destroy all aviaries found infected. The aviaries breeding the birds shipped to Cleveland were all laboratory tested within the past year and found free of infection. Our percentage of aviaries found infected during last year's testing was very low (less than 5%), and these were destroyed completely under supervision. We feel that until laboratory testing is required of all shell parrakeet breeding aviaries in the United States, such problems will continue to arise."

In all probability the infection was introduced from sources other than California and birds from the latter state subsequently became infected here.

Summary. Five patients ill with psittacosis were treated with sulfapyridine and some with sulfathiazole as well. It could not be stated that the patients were benefited by the use of either drug.

We are grateful to Dr. K. F. Meyer of the George Williams Hooper Foundation in San Francisco who ran the psittacosis complement-fixation tests and directed that the parrakeets collected by our Health Department be tested for the presence of the virus.

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THROMBOPHLEBITIS WITH MULTIPLE PULMONARY EMBOLI

PSYCHIATRIC SELF-OBSERVATIONS

BY FREDERIC WERTHAM, M.D.

MENTAL HYGIENE CLINIC, QUEENS GENERAL HOSPITAL, NEW YORK CITY

THE method of introspection has much against it. In the first place, the number of cases is restricted to one, if the observer is the same. In the second place, there are many sources of error. We all have a certain image of ourselves, and what does not fit into that picture we may overlook in any introspective efforts. For example, one may not want to admit that one is afraid and so may overlook the many disguises of fear. This source of error is even greater if one wishes to communicate the results of one's introspection to others. There is also the complicated problem of amnesia: some things that seem to be genuinely forgotten may be recalled very clearly when—as the lawyers put it—one's memory is "refreshed." All these sources of error are particularly great when the borderline of the abnormal is reached. Yet no one can deny that certain psychologic phenomena are open only to the introspective method.

I have decided to set down certain mental experiences that I had during a recent very severe illness. The background for my interest in this psychosomatic study is a great deal of work as psychiatric consultant in general hospitals. In such work I have found how important it is that certain psychopathologic syndromes in physical disease be diagnosed very early. It is sometimes difficult in severe cases of physical illness or in postoperative cases to distinguish minor transitory mental symptoms from beginning stages of more serious syndromes, such as depression or delirium. But from the point of view of prompt and proper therapeutic steps it is very important. I believe my own introspective experiences during the course of a severe physical disease are significant for the practicing physician and also have some importance for the theory of psychopathology.

Some of these experiences of mine, which I would classify as distinctly abnormal, have never been described from inside. The so-called phenomenologic school of psychopathology promised us such studies in general and theoretical articles, but has actually furnished little that is valid or practical.

I developed a thrombophlebitis in the right leg without known cause and during a period of excellent health and activity following a vacation. Under the treatment of a private physician I followed a course of complete bed-rest for about 3 weeks. Then what was evidently a small pulmonary embolus was followed within a week by further pulmonary emboli. Altogether there were probably 3 or 4. I developed a high temperature, took sulfa drugs, lost all appetite, became very toxic. When taken to the hospital I was in a very critical condition. Within a few hours after reaching the hospital I had an emergency operation, a ligation of the right femoral vein. The same night a course of penicillin was begun. Owing to the fact that the thrombus extended very high and that there was an anomaly in the location of the blood-vessels, which were deeper than usual and differently placed, the operation was more difficult and lasted longer than usual. It was carried out under local anesthesia, preceded by scopolamine, $\frac{1}{150}$ gr., and morphia, $\frac{1}{6}$ gr.

I deliberately refrain from giving surgical or medical details of my case history. They are not pertinent to the points I want to make here. The emphasis of the discussion of the first operation and a few days following it is more on the qualitative aspects, and less on the causative aspects, of the mental state. It would be difficult to isolate the causes exactly. There were present high fever, a general

toxic condition, scopolamine. It is important to emphasize that emotional factors played no part—or an insignificant one—in this condition.*

My experiences confirm the generally known psychologic law that one is apt to forget unpleasant experiences and remember pleasant ones. Two factors have become clear to me with regard to this amnesia. In the first place, pleasant or indifferent experiences are, of course, forgotten, too, in such circumstances of severe physical disease. Secondly, there are two types or kinds of amnesia: forgotten experiences that cannot be recalled even when one's memory is refreshed and those that are recalled easily. I have been told of some more or less indifferent things which I said that I have completely forgotten. I have been told of others which I seemed to have forgotten but which then I immediately recalled.

For long periods of time during the first operation I was in a state of sleep, or at any rate without full consciousness. At other times I was fully awake and clear. My main concern was with pain. It seems to me extraordinary how much I have forgotten about this pain (now, many weeks later). But I have not only a distinct memory of a memory of the pain, I have also notes to go by, notes which I dictated soon after I got a little better.

When I had this pain during the operation it filled my whole mind. There was literally no room for anything else. It is difficult to verbalize these pain experiences. For considerable periods when I was clear there would be no pain at all. Then suddenly it would come. On account of the danger of further emboli, spinal anesthesia was contraindicated. As I understand it, the deeper structures are less accessible to local anesthetics, and certain types of pain, like that of actual ligation, are not susceptible to complete anesthesia at all.

It is hard to describe one's emotional reaction to pain. It is partly a fear of more pain to come, of its continuing or getting worse; partly a hope that pain will cease (which, of course, it often did) or lessen, the "speranza di minor pena" Dante wrote about. Of this, more later.

During the first operation my attention was focused on concern with my body. Freud made a well-known statement about the distribution of "libidinal interest" in physical illness: "It is universally known and seems to us a matter of course, that a person suffering organic pain and discomfort relinquishes his interest in the things of the outside world, insofar as they do not concern his suffering. Closer observation teaches us that at the same time he withdraws libidinal interest from his love-objects: so long as he suffers, he ceases to love. . . . The sick man withdraws his libido back upon his own ego, and sends it forth again when he recovers."[2]

It is true, according to my recollection, that my libido certainly was withdrawn to my body and my interest in the outside world was decidedly restricted to what had direct bearing on my immediate situation. But in the midst of the operation, during a period when I was either anticipating pain or enduring it, I asked one of the physicians standing near me to find my wife downstairs and tell her everything was going fine. This preoccupation must have been very strong because after this physician had carried out my request and told me about it, I sometime afterward

* This statement requires some explanation: before the operation, when one embolus followed the other, during the operation and immediately after it, I was in danger of death. As a physician I should have known that merely from the objective medical symptoms, which I understood intellectually. It should have been even clearer to me when the director of the surgical service came from some distance to do the operation at once as an emergency on a Sunday afternoon, and when the head of a medical service also came on a Sunday afternoon, to see me at once. Moreover, I remember the serious faces of some of my medical friends who were there at the time. But I interpreted their concern as sympathy with the pain the emboli were causing, and at no time before, during or within a few days after the first operation did the idea even remotely enter my consciousness that I was in danger of dying, as I now know I definitely was. One might interpret this as a sort of protective mental amblyopia.

asked him the same thing again. This would indicate, in the light of my experience, that Freud's formulation is an oversimplification of very complicated levels and processes of emotional thinking.

During the periods when I was conscious and there was no pain, my intellectual capacities were greatly reduced. Some medical friends were standing near me during the operation (I was separated by a screen from the operating surgeon). On a number of occasions they talked to me in an effort to cheer and encourage me. Most of what they said was away over my head. I simply did not understand what they meant, though I heard their voices very clearly and was aware of their words, the finer modulations of their voices and their friendly intent.

The contrast between my keen awareness of the modulation of voices and my lack of intellectual understanding of what the voices said astonishes me now. At that time, however, the fact that I did not understand most of what was said to me caused me neither surprise nor anxiety. It seemed to me self-understood. For example, one doctor remarked to me—and I recognized the friendly, humorous tone—"Just like a psychiatrist, you are constituted peculiarly." (He was referring to the anomaly in location of the blood-vessels which caused prolongation of the operation.) Ordinarily this is the type of joke I would enjoy; but I understood then neither the joke nor the meaning of the sentence. Yet I took it for granted that I could not understand and asked no question. It was as if I were a child or an infant among grown-ups.

Mannheim, an author who made experiments with scopolamine upon himself, mentions among other things, "deterioration of comprehension and of intellectual performance."[3] My experiences throw a clearer light on the nature of this disorder of comprehension. Toward the latter part of the operation the anesthetist removed the gauze that was over my face, because she felt I was getting too warm. As I looked sideways I saw a large clock on the wall. I remember distinctly what was in my mind. I thought the operation was lasting very long and I was fervently hoping it would be over soon. I thought I would read the time on the clock, figure out at what time I went up to the operating room, and then I could figure out about when the whole thing would be over.

When I looked at the clock, I saw numbers in a circle. I recall particularly the 6 and the 7. I said to myself that the position of the numbers on the clock—at the top, the bottom or the side—had a meaning for telling time. But I could not figure out how. I remembered that each number meant something. But I was not sure how one picked a special number. I do not know whether or not I saw the clock's hands. At any rate, I did not comprehend that they pointed to the numbers. According to my memory, I spent considerable time trying to make out this clock. What surprises me now is how indifferent I was at my inability to solve it. I have no recollection of any anxiety in connection with this lack of comprehension. My attitude was: This is the sort of thing well people know about, and it is quite natural that I do not.

Neither did it occur to me that the whole problem I was working on was meaningless, since I had no idea of what time it was when I had been taken to the operating room, and since I had no way of knowing anyhow how long the operation[4] would continue.

Diagnostically, my inability to read the clock was a form of agnosia. Agnosia is a symptom which we know best from organic lesions in the occipital lobe, such as occur frequently, for instance, in carbon monoxide poisoning.[2] I could recognize the object, know its name, differentiate its details, but could not apperceive it as a whole nor make use of its function. I conclude from this that definite disorders of the higher processes of perception such as agnosia may be a component of the disorder of comprehension in scopolamine intoxication.

I remember only two factors which

alleviated my general feeling of insecurity while on the operating table. One was the voice of the operating surgeon and one was the reassurance derived from definite physical contact.

The surgeon's voice was deep, calm and authoritative. It was not raised at any time. One episode was characteristic of my mental state. I developed a very disagreeable pain in the right calf during the operative procedure. Somehow it seemed to me that this was due to my leg "falling asleep," as if it were in an awkward, hanging position from the knee down. (Not true, of course.) I remember that several times I moved the leg, seeking to ease its position—not exactly an appropriate behavior in the situation. I recall very distinctly the surgeon's voice saying quietly but definitely: "Don't move your leg, Dr. Wertham." My emotional response to this remark is difficult to describe. From that moment on, it was unthinkable that I should move my leg, however it felt. The remark had such an authoritative effect on me that—pain or no pain, impulse or no impulse—the idea of moving my leg did not come up again. I would venture the speculation that the building-up of the ideal ego in the very young child or infant comes about by a mechanism comparable to this response.

The second factor alleviating my insecurity was even more unexpected, had I been asked before the operation. Words spoken by medical friends present at the operation—even words I understood—had relatively little helping effect. But physical contact did have. One woman physician who assisted at the operation had to lean over me in such a way that she touched my arm. I remember her asking me at one time whether I minded that she had to lean over my arm and my reaction of astonishment at the question. I tried to figure out how to tell her what a great help it was to me. But in my over-anxiousness to make it clear to her, I could find no words at all. Much later she asked a second time and then I asked her to stay as she was. (She was actually performing a difficult, prolonged task of retraction.)

Another woman doctor present at the operation touched my forehead once and said something, and I remember her touching me as a soothing event. Evidently friendly physical contact of this primitive type is not sufficiently recognized as a helpful procedure. I have since spoken to physicians who have undergone operations or performed them and they have confirmed my own experience in this respect.

My general mental condition during the operation and during the next 2 days and nights was much the same, with very little interest in the outside world. What preoccupied me most was what I would call pressures within the body. I had the typical postoperative difficulty in urination, a great difficulty of peristalsis, with gas formation, and some difficulty in breathing. All these pressures, as far as sensation goes, seemed to combine into one.

If I tried my best to answer a question about what my mood was during this period, I could not answer. One young doctor who gave me penicillin said, "In those days you were in the carrot stage." But the facial expression—mostly on account of pain—was apparently one easily confused with that of depression. As a matter of fact, one young physician said when he saw me again a few weeks later, "Well, now you're not gloomy any more." This shows a type of misjudgment important for the psychiatrist who does consultations in a general hospital and for the general practitioner. Actually, I was then in a stage far below that where there can be such clear-cut, differentiated emotions as depression with a content of intellectual worry.

At no time during this period were there any delirious or delirioid features. But one evening I thought I was confused. When the nurse who had looked after me following the operation came on duty the next day, there seemed to me something

strange about her. I was not sure whether she was the same person or not. She looked different, and I remember thinking that maybe I was mixing people up. I asked her. She laughed and said: "I just had a permanent wave." And so I was reassured.

While such comparisons should not be carried too far, the whole condition I have been describing invites one to view it in analogy with the mental state of a very young child who lives in a world of adults who talk of things he does not understand, hears words not always comprehended, reacts quickly to modulations of voices and physical comforting.

While I was still in a very serious physical state and a very reduced mental state, I had a dream. Later I interpreted it by free association.* When I woke up from this dream it seemed it had great significance for my life. Only a fragment of this dream and its interpretation are of interest here.

"I was talking to President Roosevelt. There was a question of what kind of speech he should make. I advised him to make about the same speech he had made a year ago, but to leave out the introduction. He took my advice, but added that he'd have to make an introduction which would take at least an hour. I advised him against this introduction. He offered me a cigarette. I told him I did not smoke."

Complete interpretation even of this fragment would be too long here. At first my free associations to Roosevelt seemed to lead me nowhere. Suddenly I realized that the President in this dream symbolized a man who had lost the use of his legs but carried on successfully despite it. In the dream, my being with the President was a grandiose idea; no less a person would do. In addition, further to exalt my ego, the situation is one in which he seeks my advice and I tell him what he should do. Obviously there was a compensatory mechanism at work at a time when my ego was crushed. This mechanism meant a rallying of the ego. Such compensatory dreams in response to physical insult have been discussed by Federn.[1]

The question of offering me a cigarette is a sign of cordiality; my saying that I do not smoke was tantamount to saying that I was a "good boy." Actually, I had stopped smoking over a year before. The question of smoking had been brought up by the doctors who examined me in the hospital, and therefore had considerable emotional interest for me. Other aspects of the interpretation of this "cigarette scene" in the dream are unimportant here.

There is also the angle that in the dream I tell myself: suppose I can't ever walk again; I can shift my abilities to the intellectual sphere to make up for what I will lose in the physical sphere.

From the many ramifications of this dream one more part has to be mentioned. I had this "recovery dream" while I was still very ill. But if this interpretation so far is correct, there would seem to be an interesting error. With me only one leg was affected; whereas with the President there were two. As a matter of fact, on the basis of slight sensations there, a vague fear of phlebitis in the other leg had been in my subconscious mind. In other words, this compensatory dream came at a moment when I feared the worst. The dream said: "even then, it won't be so bad."

Soon afterwards thrombophlebitis did become manifest in the left leg, and femoral ligation was carried out in that leg, too. Before the operation I received scopolamine, $\frac{1}{100}$ gr., and morphine, $\frac{1}{4}$ gr. The second operation also presented some complications and lasted longer than usual. My mental state during this operation was so abnormal that it deserves description.

I remember the very beginning of the operation and my general apprehension. But some time later I can still hear myself addressing the operating surgeon (whom I could not see): "I feel very frivolous,

* I discussed this dream and my free associations to it with Dr. Emil Gutheil.

Dr. D." This was a most abnormal statement to make. In the first place, I had and have the greatest respect for this surgeon and would not address him like that—certainly not during an operation. In the second place, I would say that "frivolous" was about the last word that would describe my mental state at that time.

From then on throughout the operation I laughed, told all sorts of funny stories and made puns. A considerable number of my medical friends were present in the operating room. They laughed at my jokes and told funny stories of their own. It all sounded very gay. On many occasions during this operation I suffered terrible pain. I tried not to show it, but could not help contorting my face and exclaiming "Ouch!" on a number of occasions. Anybody who did not see my face would think I was having a good time. One nurse, on the other side of the screen during the operation, told me later: "You were so cheerful and took it all so easily. I have never seen anything like it."

This state of mind has to be sharply differentiated from that of a manic or hypomanic. It is characteristic of a manic that he thinks things funny that are not funny at all.[5] My jokes and puns were funny, and would have been appropriate had the situation been different. I also laughed heartily—and at the right moment—at the stories of others. There was no flight of ideas and no simple sound associations. An example of the pun I made: The pain after the first operation was relieved greatly by demerol. So I said during the second operation: "I have a new slogan. Don't get demoralized; get demerol-ized."

Toward the operation's end I suffered particularly severe pain during the ligation of the larger vessels. As I recall it, I was really in agony. At that worst moment, the internist who had been most appreciative of my actual pain, and helpful about it, saw my contorted face and said, "Anybody can tell stories like you did. *Now* is the time to tell us a really good one, from your life as a psychiatrist."

If I were asked according to my best psychiatric judgment and according to my best knowledge of myself whether I would have been able to tell a funny story at that time or whether I could have even forced myself to smile at anything then, I would have denied it without hesitation. Yet fully preoccupied as I was with pain, I immediately told a story with great gusto and with all embellishments. This was the story. As a young doctor in Hopkins, I spent a vacation with a psychotic millionaire and his male nurse at a lodge in New Mexico. We had all our meals together in the general dining room. I noticed that when the waitress served us her hands trembled noticeably. After a few days of this, I asked her whether something was wrong. She said: "Well, it's like this. I know one of you is crazy, but I don't know which one it is."

There is evidence here of clear dissociation between actual mood and behavior. In general, my insight into my condition was very poor. I did not think of my behavior as being caused by a drug, although intellectually I might have guessed that. Yet I evidently had lucid moments with psychologic insight. For instance, at one moment I said to the surgeon, as if to excuse my "frivolity": "What I am really doing is whistling in the dark."

The term *euphoria* does not cover the whole of my behavior because at times I spoke seriously of serious things. In response to remarks made by physicians near me, I made true but most indiscreet comments on the treatment of mental patients in New York and where I believed the responsibility lay.

There were a number of things which I thought I'd only had in mind but which I was later told I had said aloud. There was also an incident where I *did* something which according to my memory I had only thought and talked about. When the operation was over I thought of getting up from the operating table, walking

across to the stretcher (which I thought was across the room) and getting up on it. This was a complete misunderstanding of the situation. I was in no condition to get up and the stretcher was right next to the operating table. I learned later that I actually attempted to sit up with this purpose in mind, and lay still only when told to do so. A few hours after the operation I returned to my normal state of mind and realized how abnormal my behavior had been.

The mental condition during the operation was a form of scopolamine psychosis. It was characterized by euphoria, overtalkativeness, general lack of inhibition, euphoric misjudgment of the situation, side by side with more or less clear consciousness of apprehension and pain and flashes of insight. There were no hallucinatory, delirious or dream-like experiences. This particular form of scopolamine psychosis with such a dissociation within the mental life I have not seen described before. It is probably only by self-observation that such a contradictory psychologic syndrome can be delineated; but it can be diagnosed objectively.

Actually, the euphorization of my behavior was a great help. What did it accomplish? It seems to me that it counteracted the anxiety which was undoubtedly present. While telling jokes or listening to them, I was distracted from anxiousness and the strain of experiencing pain. Such a contrast between euphoria and anxiety occurs in experimentally induced mescaline psychosis, as shown by the retrospective accounts of subjects.[6]

With regard to the subject of pain and analgesics, some of my observations are significant. I believe that in studies of pain, the threshold of pain is too much emphasized. Actually, the *quality* of pain is very important. I could, after this operation, have enumerated six or eight different kinds of pain, each sharply distinguishable from the other in quality. To express them in words would be impossible. Had I given each of these pains as they occurred a number, I believe an observer would have found that I could have identified by its number the special type of procedure by its accompanying kind of pain.

Some of the qualities of pain are: (1) Localization (some I could not have localized at all; some I think I could have indicated exactly). (2) Duration. (3) "After-image" (I use this for want of a better term, because some kinds of pain continued even after I knew they were over. This is comparable to the phenomenon of after-images and eidetic images in visual perception. Such phenomena are easier to investigate in the sphere of vision, but exist also in other forms of sensation. It is possible that this type of pain refers to a more primitive, undifferentiated kind of sensation.[7,8] (4) Special qualities of pain, as when a nerve is touched. (5) Association with fear (some types of pain seem to be more associated with fear than others).

If psychologic factors play a great rôle in physical disease, as I believe they do, it may well be indicated to stimulate the productive activity of patients in the early stages of their physical disease. I believe that my interest in dictating these observations at the time (they were much more detailed than this paper would indicate, and the paper itself was written during my hospital stay) helped me to rally the recuperative forces of my organism. As Heine said:

> "It was disease—the truth to tell—
> Which gave impulse to my creation.
> Creating, I got better.
> Creating, I got well."

From a practical point of view, this study shows that there are definite and diversified psychiatric aspects of physical disease. Physicians are apt to neglect such experiences, but they are a grim reality. The psychopathologic aspects of physical disease demand and deserve attention. They may make the difference between life and death.

Medical and surgical patients need

psychologic advice about how they should act, what their expericnees mean; they need psychologic preparation for what to expect; they need guidance so that they can make the best of the possibilities. As a physician, I was less handicapped in coping with these experiences than the general patient.

All these psychologic and psychopathologic features of physical disease are a part of medical and nursing care. It is a problem that can be attacked along three levels: The first is the part of the nurse. The second is that of the medical man and the surgeon. The third is the part of the psychiatrist, who should be available for the diagnostically doubtful, the more severe and prolonged abnormal manifestations. Here is one phase of psychosomatic medicine which can be put into practice immediately without waiting for further investigation. Only in this way can psychiatry be really integrated in a general hospital.

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THIOURACIL EFFECT IN DIABETES MELLITUS COMPLICATED BY HYPERTHYROIDISM

By William S. Reveno, M.D.
ASSISTANT PROFESSOR OF CLINICAL MEDICINE
DETROIT, MICHIGAN

(From the Department of Medicine, Harper Hospital and Wayne University College of Medicine)

Control of diabetes complicated by hyperthyroidism has always presented a difficult problem. Thyroidectomy has on occasion arrested the diabetes, rarely if ever cured it, and mostly rendered it less severe. Now comes thiouracil with its established positive action in controlling hyperthyroidism, offering the opportunity to observe its effect in ameliorating the profound action of hyperthyroidism and diabetes.

Six patients presenting this condition have been treated with thiouracil to control the thyrotoxicosis and the experience is described in the following detailed report:

Case Reports. Case 1. T. J. D., a physician, aged 64, was first seen in September 1944 because of palpitation, sweating, exhaustion, tremor and a weight loss of 28 pounds during the past year. He had been under treatment for cardiac decompensation earlier in the year and was now on a daily maintenance dose of 3 gr. digitalis leaf. The diet, to which he claimed close adherence, consisted of P 70, C 150, F 150, with a single daily dose of 40 units protamine zinc insulin. Glycosuria was persistent in spite of these measures.

The diabetes antedated the hyperthyroidism which was first discovered about 20 years ago. Treatment with Lugol's solution was continued for 5 years and then stopped because of little benefit.

The patient was short, paunchy and gray-haired, with slight exophthalmos, lid-lag and conjunctival congestion. There was no palpable thyroid nor was substernal enlargement revealed by Roentgen ray. The palms were warm and moist with a fine tremor of both hands. The heart was normal in size, the sounds were distant, the rate was 100 with normal rhythm, and there were no murmurs. The prostate gland was smooth and both lateral lobes were enlarged.

The blood pressure was 120/100, the weight 187 pounds and the height 65 inches. The fasting blood sugar was 254 mg. %, there was a 4+ glycosuria and the BMR was +21%. Laboratory studies were otherwise within normal limits.

Digitalis was discontinued and thiouracil, 0.2 gm. 3 times daily, started. Three capsules of concentrated mixed vitamins were to be taken daily. Diet and insulin were continued as before. At the end of 2 weeks he reported less nervousness and agitation. In another 2 weeks the sweating had stopped and the tremor was gone; a fasting blood sugar was 166 mg. %, and the BMR was +26%. After 6 weeks of treatment all of his original symptoms had gone, he had gained 5 pounds in weight, the BMR was +14% and the urine had been sugar-free during the last 2 weeks. (He was examining 4 specimens daily.) The thiouracil was reduced to 0.2 gm. twice daily and insulin dosage cut to 30 units PZI daily. In another 2 weeks the BMR was +10%, the weight had increased another 3 pounds and the glycosuria continued. A fasting blood sugar was 104 mg. %. He was entirely symptom-free. Insulin was reduced to 10 units PZI daily and the thiouracil to 0.1 gm. 3 times daily, but at the end of 2 weeks the BMR was +23% so the thiouracil was increased to 0.1 gm. 4 times daily which has since been continued as a daily maintenance dose. The insulin was discontinued at this time (after 10 weeks treatment) and the diabetes has remained controlled by diet alone. Several fasting blood sugar determinations made at monthly intervals were 114, 136, 125, 121 and 118 mg. %. The BMR has ranged between −2 and +12% and reached +23% once when the dose of thiouracil was reduced to 0.3 gm. daily. The thyroid gland, which could not be palpated, developed bilateral palpable enlargement during the 8th month of treatment.

After 9 months treatment this patient is symptom-free. He has gained 13 pounds, his BMR is +10%, and to all appearances

the thyrotoxicosis is in remission and the diabetes under satisfactory control.

CASE 2. R. B. K., white male, aged 45, has been under observation since December 1935, when he first developed weakness, polyuria, polydipsia and weight loss of 15 pounds. In November 1933, he had developed the full-blown picture of exophthalmic goiter and thyroidectomy was performed in January 1934. This was followed by improvement until July 1935, when the goiter returned along with many of the previous symptoms. Lugol's solution controlled this disturbance for the next 4 months and then, following an attack of sore throat and "intestinal flu," it lost its effectiveness and he started a downhill course which terminated with symptoms of diabetes.

The patient was short, stocky and overly alert. The breath had an acetone odor. There were marked exophthalmos and lid-lag, bilateral smooth thyroid enlargement, tachycardia and warm moist palms with fine tremor. The tonsils were badly infected and the teeth decayed, with marked gingivitis. The blood pressure was 150/90, the BMR +32%, and a fasting blood sugar 190 mg. %. He weighed 135½ pounds.

He was hospitalized for 1 week during which he responded well to bed rest, diet and insulin. When discharged he was on a diet of P 73, C 118, F 135, with 25 units regular insulin 3 times daily. This was gradually reduced to 10 units 3 times daily during the next 2 weeks. Lugol's solution was now resumed and the improvement further accelerated. Within 1 month the weight had increased 5 pounds, the BMR was +24%, the urine showed only occasional traces of sugar and the goiter symptoms had largely subsided. At the end of another month the condition had improved markedly and tonsillectomy was performed without mishap. He continued to gain steadily, the diabetes soon was controlled without insulin even with a gradual increase in the carbohydrate and fat of the diet. The hyperthyroidism continued in remission while taking 3 drops Lugol's solution daily. This satisfactory state continued 3 months, when glycosuria reappeared requiring 17 to 20 units regular insulin daily for control. In December 1936, the regular insulin was replaced by 10 units of protamine insulin but control was unsatisfactory. During January 1937 a dose of 7 units regular insulin was given in the morning and 8 units crystalline insulin (Stearns) in the evening, again with unsatisfactory results. Successively protamine insulin, 2 doses daily, was tried, followed by 1 dose of protamine in the evening and 1 of regular insulin in the morning; then the 2 were given at the same time in the morning and this appeared to effect better control although the dosage had to be increased to 10 units regular and 20 units protamine. This latter was replaced by protamine zinc insulin in January 1938.

Control of the diabetes was nevertheless far from satisfactory and although the thyrotoxicosis appeared controlled a loss of effectiveness of the Lugol's solution was feared as was the development of a state of iodine fastness or resistance. Since the patient objected to thyroidectomy, a course of 6 Roentgen ray treatments was administered during a period of 3 months in late 1938 and early 1939. There was no evident change following this therapy. The thyroid which had previously diminished in size and increased in hardness with the continuous iodine therapy now became somewhat smaller. Exophthalmos, tachycardia and tremor reappeared gradually, the BMR reached a level of +50% and the diabetes required increasing doses of insulin for control (35 units regular and 35 units PZI daily).

Thyroidectomy was performed in November 1939 and the patient made an uneventful recovery. The diabetes, however, did not improve, in spite of the abatement in thyrotoxicosis. Control became increasingly "hair trigger" and was now more and more difficult, requiring varying and increasing amounts of both regular and protamine zinc insulin. To add to these difficulties, exophthalamos of the right eye began to develop 6 months after thyroidectomy and, although it appeared advisable to administer thyroid extract for its control, this was not done for fear of further disturbing the diabetes.

The unilateral exophthalmos increased during the next 6 months, the blood cholesterol reached a level of 344 mg. % and the BMR −15%; the weight increased 6 pounds and there was now sensitivity to cold with sluggishness, and puffiness of the upper eyelids. Frequent hypoglycemic reactions alternated with high blood sugar levels and almost constant glycosuria. ½ gr. thyroid extract daily was started and striking improvement of all symptoms followed after

1 month. With increase to ½ gr. thyroid extract twice daily the improvement was maintained without appreciable change for the next 3 years and 10 months, although the diabetes now required 50 units PZI and 6 units crystalline insulin daily for fair control that was interspersed with frequent hypoglycemic reactions. (Globin insulin was tried for a time without success.)

In December 1944 there was noticeable nervousness and exophthalmos with tremor, tachycardia and warm moist palms. The BMR was +9%. (Thyroid extract had been discontinued 1 month before because of a suggestion of nervousness, tremor and mild tachycardia.) Thiouracil, 0.1 gm., 3 times daily, was started and within 4 weeks the symptoms had abated and the BMR was −16%. The dosage of thiouracil was reduced to 0.1 gm. twice daily and continued at this level for the next 6 months, the BMR varying between +7 and −1%. With an increase to +11% early in June 1945, thiouracil was increased to 0.1 gm. 3 times daily which is the present maintenance dose.

In the 6 months of thiouracil therapy the weight had increased 16 pounds and all evidence of thyrotoxicosis, including exophthalmos, had disappeared. The diabetes was somewhat less severe in that a fair measure of control could be maintained with 38 units PZI and 10 units crystalline insulin daily.

In this patient with primary hyperthyroidism that antedated his diabetes, improvement in the latter condition followed initial dietetic restriction, insulin and Lugol's solution. Gradually, however, even under continued iodine administration, then Roentgen ray therapy, thyroidectomy and finally thiouracil, the diabetes slowly increased in severity and now, despite the remission in the thyrotoxicosis, it still presents a difficult management problem.

Case 3. C. C., white male, aged 41, first came under observation in January 1936, when he had an acute upper respiratory infection with right-sided pleurisy and effusion. He had had diabetes mellitus for 8 years, was not adhering closely to his diet and was maintaining varying control by using 50 units regular insulin divided into 2 doses. There was fever and acidosis and the blood sugar level was 388 mg. %. Large doses of insulin and ample fluids cleared the acidosis and gradually brought the diabetes under control. However, following release from the hospital he continued to show marked fluctuation in blood sugar level and was having frequent reactions in spite of redistribution of the diet (P 70, C 150, F 130) and variation in dosage and timing of insulin. He was shifted from regular to crystalline, to protamine and to protamine zinc insulin at the time when these first became available. A fairly good degree of stabilization was finally achieved in September 1937 by the administration of 30 units crystalline insulin in the morning and 20 units 12 hours later. He gained some weight on this régime but began to manifest nervousness and a slight tremor of the hands in November 1937. The skin was warm and the palms moist, but there were no eye signs, the thyroid was not palpable and there was no tachycardia. The blood pressure, however, changed from a range of 110 to 140 systolic and 60 to 90 diastolic to 150 to 170 systolic and 80 to 90 diastolic. The BMR was +22%.

A course of physostigmine salicylate, $\frac{1}{32}$ gr. 3 times daily, was followed for 15 months without effect on the hyperthyroidism. Shortly after discontinuing this treatment and following a change in jobs to one requiring greater physical exertion hypoglycemic reactions increased and crystalline insulin was reduced to 20 units every 12 hours. There were fewer reactions and the control of the diabetes was fair for the next year although there was a gradual loss of 14 pounds in weight, with tachycardia, tremor, sweating and a high pulse pressure. There was still no palpable thyroid or characteristic eye signs. Two BMR determinations made 1 week apart were +35 and +41% (1940). Three drops Lugol's solution were given daily and at the end of 2 months the BMR was +16%, the tachycardia was diminished, sweating and tremor had stopped and there were fewer hypoglycemic reactions. At this time (1940) Althausen[1] announced the galactose tolerance test for differentiating glycosuria of diabetes mellitus from that due to hyperthyroidism. The test was performed on this patient with a reading of 34.72 at ½ hour and 38.44 mg. % at the end of 1 hour —indicating the presence of hyperthyroidism.

The patient continued taking 3 drops Lugol's solution daily and 20 units of crystalline insulin every 12 hours for the next 41 months. He regained his lost weight,

and his diabetes was quite well controlled. At this time the thyroid gland became palpable and both lobes felt nodular.

Thiouracil replaced the Lugol's solution in August 1943 and was given in a dose of 0.2 gm. 3 times daily. The BMR at this point was +13% and the blood cholesterol level 250 mg. %. A slow rise in the BMR followed, readings taken every 2 weeks being +14, 10, 18 and 26%, with no change in the general condition. This unusual reaction to thiouracil may have been due to the prolonged iodization but subsequent failure to effect a lowering of the BMR throughout a 20 month period of observation, even with doses of thiouracil up to 1.2 gm. daily, and substitution of thiourea for thiouracil, is not easy to explain. The patient either must have an inherent resistance to these drugs, or one acquired through the prolonged administration of iodine; or the elevated BMR may indicate disturbed metabolism other than that due to hyperthyroidism. With the latter condition in remission, failure to respond in expected fashion becomes understandable.

Since discontinuing treatment for the thyrotoxicosis and with only diet and insulin, there has been maintenance of weight and no evidence of hyperthyroidism, while the diabetes has remained well controlled.

In this patient with the diabetes present before the secondary hyperthyroidism, remission of the latter condition through the use of iodine has made possible smooth, effective control of the diabetes. An attempt to substitute thiouracil and thiourea for the iodine met with failure due to resistance, possibly natural, but more probably due to the prolonged iodization and the presence of a state of remission (in spite of an elevated BMR).

Case 4. C. M., a white female, aged 50, first came under observation in May 1944 because of increasing pallor, weakness and anorexia during the previous 6 months, and an attack of nausea and vomiting during the previous 24 hours. She had had a thyroidectomy for exophthalmic goiter in 1928, a tonsillectomy the same year, a hysterectomy in 1934, an attack of arthritis in 1938, and diabetes of short duration successfully controlled by diet alone, in 1942.

The skin had the characteristic waxy yellow color of primary anemia. There was no palpable thyroid tissue and no exophthalmos or tremor. There was a rough systolic murmur at the apex, normal rhythm and an increase in rate. The reflexes were normal. Laboratory studies revealed achlorhydria; hemoglobin 45% (Sahli), with r.b.c. 1.55 million (color index of 1.5) and marked anisocytosis. With absence of parasites and occult blood in the stool and negative findings on Roentgen ray study of the gastrointestinal tract, a diagnosis of primary (Addisonian) anemia was warranted and was further confirmed by the characteristic reticulocyte response that followed the parenteral use of liver extract. She remained in the hospital 12 days and improved markedly while there.

A fasting blood sugar was 192 mg. % with the urine negative for sugar 2 days after admission. A BMR was +27% and a blood cholesterol 277 mg. % on the same day. The day of discharge the BMR was −5%. The weight was 172 pounds.

Improvement continued with weekly injections of 15 units concentrated liver extract and at the end of 8 weeks the red cell count had reached a level of 5.46 million and the hemoglobin 86% (Sahli). Progress was uneventful until December 16, 1944, when she complained of insomnia, shakiness and trembling. There was a weight loss of 2 pounds in the past month, the blood pressure was 146/80, and the pulse rate 100. A fine tremor of the hands was present. With mild sedation during the following month, she reported improvement but had lost another 2 pounds. The pulse was still rapid and the tremor of the hands marked. In February 1945, although she still reported improvement, she had again lost 2½ pounds, the tremor was still present, the pulse rate was 136 and the BMR +22%. There were no eye signs and no palpable thyroid tissue.

One-tenth gm. thiouracil was administered twice daily during the next month. By March 23, 1945, she had lost another 2 pounds, but the BMR was now +17%, the pulse rate 100, blood pressure 110/70, and there was no tremor or nervousness. Thiouracil was increased to 0.1 gm. 3 times daily. One week later she began to notice increasing urinary frequency, then polyuria, polydipsia and finally vaginal pruritus. When seen on April 20, she had lost 7 pounds, the fasting blood sugar was 258 mg. %, there was marked glycosuria, but no tremor or nervousness and no tachycardia. The hemo-

globin was 104% (photoelectric) and r.b.c. 7.01 million. The blood pressure was 120/80 and the BMR was now +3%.

This turn of events, a flareup having every appearance of a true diabetes mellitus following closely upon the thiouracil induced remission in the hyperthyroidism, strongly suggested stimulation of the anterior pituitary not only to produce more thyrotropic hormone but to augment its contra-insular action. This sudden precipitation of diabetes seemed analogous to that which develops in Houssay animals by the injection of anterior lobe extracts, with protein constituting the sole source of the excreted glucose.[7]

The use of insulin was deferred and a diet consisting of P 80, C 100, F 40 prescribed, with the thiouracil continued as above. Two weeks later, May 4, 1945, there was a 3 pound weight loss, a fasting blood sugar level of 193 mg. %, decreased glycosuria, and a marked diminution in the polyuria, polydipsia and pruritus. The BMR was now+20% but there was no nervousness, tachycardia or tremor. In 2 more weeks (May 18) the weight had fallen another 4 pounds but the fasting blood sugar was 160 mg. % with no glycosuria and no diabetic or hyperthyroid symptoms. The BMR was now +5%. During the next 6 weeks the weight dropped $5\frac{3}{4}$ pounds, she was aglycosuric with a fasting blood sugar level of 169 mg. % and was feeling fine with no subjective or objective disturbance. The BMR was +24%. The diet was increased by 45 gm. carbohydrate but the rest of the treatment remained the same. At the end of 10 days she had regained 5 pounds and continued symptom-free. The BMR was now +15%. Apparently the disturbance, appearing first as a recurrent hyperthyroidism, then as a precipitate diabetes, was subsiding and gradual increase in the diet to supply the caloric need was being instituted while continuing with thiouracil to suppress the hyperthyroidism.

This patient with primary hyperthyroidism treated by thyroidectomy 17 years ago, developed diabetes 2 years ago which was successfully controlled by diet alone and apparently subsided. Fourteen months ago she was found to have a primary anemia that responded to specific therapy and has remained under control with continuous parenteral liver therapy. Five months ago she showed evidence of recurrent hyperthyroidism which subsided appreciably after 4 weeks of thiouracil. A week later full blown diabetes developed suddenly which is now controlled by diet alone while thiouracil is still being administered. The primary anemia continues under control by means of liver extract.

Appearance of the diabetes 5 weeks after continuous thiouracil may well have resulted from stimulation of the anterior pituitary through thiouracil suppression of the thyroid. Thus the thiouracil cannot be credited with an immediate assist and its rôle at best lies in rendering indirect aid through suppression of the hyperthyroidism.

(An interesting speculation regarding the combination of primary hyperthyroidism, diabetes and primary anemia may be offered with the liver in the rôle of chief target organ. The hyperthyroidism with the associated hyperfunction of the anterior pituitary may well have produced liver damage[6] with ultimate impairment in carbohydrate metabolism and impaired storage capacity for the intrinsic anti-anemic factor.)

Case 5. M. G., a white female, aged 57, was referred by her physician, May 29, 1945, because of difficulty in controlling diabetes mellitus which had been discovered some 6 weeks earlier. There was weakness, exhaustion, some weight loss, increased appetite, polyuria, polydipsia and vaginal pruritus. The history disclosed chorea at the age of 12; a small goiter for as long as she could remember (one BMR 8 years ago was reported normal); and treatment for hypertension during the past year.

The patient was quite nervous and her voice was tremulous. She weighed $147\frac{3}{4}$ pounds, was $63\frac{3}{4}$ inches tall, showed a slight stare with lid-lag, moist warm palms with a fine tremor, and bilateral irregular-nodular enlargement of the thyroid, partly substernal. The blood pressure ranged from 180 to 170 systolic and 120 to 110 diastolic. The eye-grounds showed very little arterial change. The fasting blood sugar was 178 mg. %, with aglycosuria. The BMR was +15%.

A diet of P 70, C 100, F 40 was prescribed and the patient started on 0.2 gm. thiouracil 3 times daily, a capsule of mixed vitamin concentrates to be taken with each dose. At the end of 2 weeks she reported decrease in nervousness, palpitation and the urinary disturbance. The blood pressure was 160/80,

the pulse rate 90, the BMR +7% and the fasting blood sugar 132 mg. %. The urine had shown only an occasional trace of sugar. The weight was down to 144 pounds and the thyroid was softer and slightly larger. At the end of another 2 weeks the weight was 139½ pounds, the pulse 76, blood pressure 140/90, BMR +7% and fasting blood sugar 139 mg. %. There was still occasional glycosuria. She was sleeping better, was less nervous, the voice was stronger and her strength was returning. No tremor or palpitation was noted. The thyroid was somewhat larger and softer.

Thiouracil was reduced to 0.2 gm. twice daily and at the last examination, July 10, 1945, the weight was 140 pounds, blood pressure 140/90, pulse 64, fasting blood sugar 128 mg. % with constant aglycosuria and the BMR −8%. There were no disturbing symptoms and to all appearances the diabetes had come under control while the hyperthyroidism was in remission.

This patient with diabetes mellitus aggravated by a secondary hyperthyroidism responded promptly to dietetic management as the hyperthyroidism was brought under control with thiouracil.

Case 6. M. M., a white female, aged 26, first complained of weakness and exhaustion in the fall of 1941. Gradually she developed polyuria and polydipsia, and lost about 10 pounds in weight by January 1942. At this time she had marked glycosuria with a fasting blood sugar level of 200 mg. %. The BMR was zero. The weight was 90 pounds.

A diet of P 60, C 125, F 100 was prescribed and she was to take 10 units PZI daily. Improvement was marked in a very short time. There was weight gain, with aglycosuria and cessation of disturbing symptoms. The diet was gradually increased to P 70, C 150, F 130 and she remained aglycosuric while taking between 5 and 7 units PZI daily. Gradually, however, control became increasingly difficult and she failed to gain weight in spite of an increase in diet to P 100, C 150, F 170, with a dose of 10 to 12 units PZI and 5 to 10 units crystalline insulin. There were occasional hypoglycemic reactions and these continued to recur during the next 20 months while she was out of the city.

On her return May 29, 1945, she weighed 95½ pounds, was still having difficulty controlling the diabetes in spite of a present dose of 12 units PZI and 22 units crystalline insulin (1 injection). A fasting blood sugar was 204 mg. %.

She was hospitalized for 10 days and although she was ambulatory it was still difficult to achieve control of the diabetes. During this time it was noted that her palms were warm and moist and showed a fine tremor. The eyes too were somewhat brighter than formerly, although there was no exophthalmos or lid-lag. Neither was there any palpable thyroid tissue. A BMR was +10% June 8, +12% June 10 and 11.

In the belief that a mild hyperthyroidism was interfering with diabetic control, the patient was started June 12 on 0.2 gm. thiouracil 3 times daily. The weight was 96 pounds and the insulin dosage was now 13 PZI and 26 crystalline units (1 injection). At the end of 1 week the weight was 98½ pounds, the fasting blood sugar 151 mg. % and she was spilling less sugar. The BMR was +11%. The palms were still warm and moist but there was no tremor. After another week the weight was 98 pounds, the fasting blood sugar 105 mg. %, there was very little glycosuria, and no tremor while the palms were now cool and dry. The BMR was +12%. The thiouracil was now reduced to 0.2 gm. twice daily. Two weeks later the weight was 100 pounds, the fasting blood sugar 63 mg. %, with complete aglycosuria. The BMR was +5%. She was feeling well and showed no evidence of hyperthyroidism. Evidently, since this was the first time in several years she had remained continuously aglycosuric for 2 weeks, it was believed that the suppression of the very mild hyperthyroidism by thiouracil had aided in the control of the diabetes.

In this patient the diabetes was difficult to control until a remission of the mild secondary hyperthyroidism was induced through the use of thiouracil.

Summary and Conclusions. Of the 6 patients, 3 (Nos. 1, 5 and 6) showed improved control of the diabetes following the remission in the hyperthyroidism induced by thiouracil. A fourth (No. 3) also showed improvement but the remission in the thyrotoxicosis had been previously induced by iodine and not by thiouracil. The remaining 2 patients (Nos. 2 and 4) failed to respond favorably to the treat-

ment, which in Patient 4 may even have served indirectly to reactivate a latent diabetes.

It is especially significant that the 4 patients who improved all had secondary hyperthyroidism (toxic adenoma) which became manifest after the diabetes had appeared. The 2 patients classed as failures had primary hyperthyroidism (exophthalmic or toxic diffuse goiter) which antedated the diabetes in each instance. Evidently this latter type of patient, in which the disturbance is polyglandular, fails to respond satisfactorily to any known form of treatment—as in the case of Patient 2 who had had two thyroidectomies, iodine, roentgen ray therapy and thiouracil.

A review of the reported thiouracil treated cases of diabetes and hyperthyroidism discloses both successes and failures. When these are classified as to type of hyperthyroidism, the validity of the above mentioned observation becomes apparent. Astwood's[2] patient with secondary hyperthyroidism, in whom the diabetes preceded the thyrotoxicosis by 10 months, was able to discontinue the use of protamine zinc insulin altogether. The patient reported by Kahn and Stock[5] had a toxic diffuse goiter antedating the diabetes which was difficult to control. Rose and McConnell's[9] patient in whom treatment failed to improve the diabetes was a 13 year old girl with primary hyperthyroidism. (This had become evident 11 months after the onset of diabetes.) They make the interesting comment that "possibly the production of increased diabetogenic activity in the pituitary by thiouracil may have prevented amelioration of the diabetes." McGavack[8] reports no expected improvement in any of 4 diabetics, and in 1 the tolerance decreased without known cause. Only 1 of the 4 patients is reported as having had toxic diffuse goiter. The type of goiter in the other 3 patients is not described.

Eaton[3] treated 4 patients who had diabetes and found that the 3 patients who responded well had secondary hyperthyroidism while the 1 that did not respond had primary hyperthyroidism. Fishberg and Vorzimer[4] report 2 diabetic patients with secondary hyperthyroidism in whom the diabetes came under better control after thiouracil therapy.

Of the 13 patients reported in the literature, 4 responded favorably while 9 failed to show improved control of the diabetes. With the 6 patients reported here the total is 19, of which 8 were improved (1 of these with iodine), and 11 not improved.

Evaluation of the effectiveness of thiouracil in this small series of cases would place it on a comparable level with thyroidectomy where the hyperthyroidism is secondary. In primary hyperthyroidism, or exophthalmic goiter, while it does control the toxicity, it exerts little favorable influence on the control of the associated diabetes.

The thiouracil was supplied by the Lederle Laboratories, Pearl River, N. Y.

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THE INFLUENCE OF ENVIRONMENTAL TEMPERATURE AND RELATIVE HUMIDITY ON THE RATE OF WATER LOSS THROUGH THE SKIN IN CONGESTIVE HEART FAILURE IN A SUBTROPICAL CLIMATE*†

By George E. Burch, M.D.

NEW ORLEANS, LOUISIANA

(From the Department of Medicine, Tulane University of Louisiana, and Charity Hospital)

The problem of water balance in congestive heart failure is relatively little understood. This is essentially true also for thermal regulation. That thermal regulation is disturbed in congestive heart failure has been established by clinical observations and in particular by the studies of Steele and Cohn,[3,9,10] although Kinsey and White[7] regard fever of more than 1° F. as being due to a complication of failure. The former group of observers noted the development of fever in uncomplicated congestive heart failure, even in the cool climate of New York City. They concluded that the elevation in body temperature resulted mainly from disturbances in the circulation concerned with the elimination of heat *via* the skin. That the rate of heat production may be increased in congestive heart failure is generally accepted. In considerations of water balance and thermal regulation the factors of sweating and the evaporation of water from the surface of the skin have been neglected. Furthermore, the influence of environmental temperature and relative humidity and subtropical and tropical climates on congestive heart failure in general, and thermal regulation and water loss from the skin in particular, have received little serious attention. It is the purpose of this report to present the results of observations conducted to understand more clearly the above mentioned phenomena.

Methods and Materials. The method employed to measure the rate of water loss was that previously described.[8] The method consists essentially of directing dry oxygen by means of suitable tubing and metal chambers[2] over known areas of skin to collect surface water. The water-laden oxygen is then conducted through aluminum coils cooled in carbon dioxide snow where the water condenses. The water collected in the coils is measured gravimetrically.

The areas studied were the tip of the right index finger, the pretibial area of the middle portion of the right leg and the volar surface of the right forearm.

The subjects rested for 1 hour in a hospital type of bed in an air-conditioned room free from perceptible movements of air. During the period of rest, the metal chambers isolating the areas of skin for study were sealed in place. The room air was comfortable during this time and during the first measurements, the conditions being: mean temperature 21.3° C., range 20 to 22.8; mean relative humidity 60.2%, range 48 to 72. The rate of water loss was then measured for the three areas (finger tip, leg, and forearm) simultaneously, three successive 15-minute collections being made. The room conditions were then made hot and humid within a period of 15 to 20 minutes. The room conditions were changed to: mean temperature 40.2° C., range 37.2 to 42.2; mean relative humidity 64.2%, range 52 to 72%. When these conditions were attained three successive simultaneous 15-minute measurements of the rate of water loss were then made for the three skin areas.

The subjects studied consisted of 11 normal adults varying in age from 22 to 41 years, 9 were males and 10 were white. There were 10 subjects suffering from various diseases (diabetes mellitus, subacute glomerular nephritis, psychoneurosis, chronic hepatitis, fever, pernicious anemia, senility and acute rheumatic fever) but free from congestive heart failure. These subjects varied

* Aided by a grant in aid by the Helis Institute for Medical Research and the Rockefeller Foundation.

† This is the 16th paper published from this Laboratory of Tropical Physiology.

from 17 to 64 years of age, 4 were males and 2 were white.

There were 20 patients who suffered from right and left ventricular congestive heart failure. These were divided according to the degree of failure at the time of study. Five patients (12 to 58 years of age, 2 males and all negro) had mild to no failure, *i. e.*, Functional Class I and II of the American Heart Association criteria for the classification of heart failure. Five patients (28 to 52 years of age, 2 males and 4 negroes) had a moderate amount of failure, *i. e.*, Functional Class III. Ten patients (30 to 65 years of age, 5 males and 9 negroes) suffered with severe failure, *i. e.*, Functional Class IV.

All of the patients with congestive heart failure had entered the hospital in Class IV failure, but some of them had recovered to Class I, II or III failure. The edema and general condition of some of the 10 patients in Class IV failure was improving, while in others the edema and general state of the heart failure was becoming progressively worse. Since it was necessary to move these patients from the wards of Charity Hospital to our laboratory at the Tulane Medical School, none of the patients were in a moribund state, that is suffering from extreme air hunger and circulatory collapse. They were not experiencing cold sweating. Three of the patients were receiving oxygen. This was discontinued during the studies without unfavorable results. All of the 20 subjects were on a therapeutic régime for congestive heart failure. This included the use of digitalis and diuretics; the latter drugs were used in only some instances.

All rates of water loss were expressed in milligrams per 10 sq. cm. of surface area per 10 minutes. The surface area of the finger tip was calculated by the method previously described.[1,6]

Results. These are summarized in Tables 1, 2 and 3, and Figures 1, 2, 3 and 4.

The mean rate of water loss from the skin of the right index finger tip, volar surface of the right forearm and anterior surface of the right leg was 10.7, 5.4 and 5.3 mg. per 10 sq. cm. of skin surface per 10 minutes respectively for the normal subjects in a comfortable environment (Table 1 and Fig. 1). The ranges were 7 to 17.7, 3.5 to 8.7 and 3.1 to 8.3 respectively. In a hot and humid environment, the normal subjects lost water from the three areas of skin at a mean rate of 28.3, 31.5 and 39.9 mg. per 10 sq. cm. per 10 minutes respectively for the finger tip, forearm and leg. This represents an increase of from about 3- to 8-fold (Table 1). In the comfortable environment, there was no visible sweating, while in the hot and humid environment, sweating was not only visible but profuse. These differences in the rates of water loss are graphically illustrated by Figure 1.

The patients with severe congestive heart failure resting in a comfortable environment lost water at a mean rate of 5.4, 4.9 and 4.4 mg. per 10 sq. cm. of skin surface per 10 minutes for the finger, forearm and leg respectively. The ranges for the 3 parts were 3.8 to 8.1, 1.6 to 7.2 and 1.9 to 6.3, respectively. In a hot and humid environment, the mean rates of water loss for the skin of the 3 parts were 13.2, 10.8 and 10.8, the range being 10.6 to 17.4, 7.5 to 15.5 and 6.7 to 19.1 respectively (Table 3, Fig. 1). These patients showed no signs of visible sweating in the comfortable environment and very little visible sweating in the hot and humid environment. The percent increase in the mean rates of water loss in the hot and humid environment for the finger tip, forearm and leg were only 46.6, 34.3 and 27.1 respectively of the rate for these three areas in the normal subjects. The relative rates of water loss in the normal subjects and patients with congestive heart failure are shown by Figure 1. The rate of water loss in comfortable environment tended to be less in the patients with congestive heart failure than in the normals.

Table 3 and Figures 3 and 4 show the rates of water loss in mild, moderate and severe congestive heart failure. As the degree of heart failure decreased, the rate of water loss in the hot and humid environment approached normal. In the patients with moderate failure, the mean rates of water loss from the finger tip, forearm and leg for the hot and humid

atmosphere were 62.5, 75.6 and 60.7% respectively of the normal rates under similar conditions. In the patients with mild failure, the mean rates were normal.

In the patients with miscellaneous diseased states other than congestive heart failure the rates of water loss in the comfortable and hot and humid atmospheres were found to be within normal variations (Table 2 and Fig. 2).

It is well to note that in all of the groups of subjects studied, there were individual instances of overlapping of rates. However, in the patients with severe congestive failure there was a consistent impairment of water loss in the hot and humid environment.

General Reaction to Hot and Humid Environment. During the course of these studies, the subjects were observed as to

TABLE 1.—THE RATES OF WATER LOSS (MG. PER 10 SQ. CM. OF SURFACE AREA PER 10 MIN.) MEASURED SIMULTANEOUSLY FROM THE SKIN OF 3 WIDELY SEPARATED AREAS OF 11 NORMAL SUBJECTS

Subject				Parts studied								
				Finger			Forearm			Leg		
No.	Age	Sex	Color	C	H. & H.	H.H.:C	C	H. & H.	H.H.:C	C	H. & H.	H.H.:C
1	26	M	W	8.6	17.8	2.1	5.6	8.3	1.5	5.6	10.4	1.9
2	35	F	W	10.4	46.7	4.5	8.7	75.6	8.7	8.3	76.8	9.3
3	22	M	W	7.0	33.6	4.8	4.0	37.7	9.4	3.1	40.1	12.9
4	24	M	W	17.7	42.3	2.4	3.5	32.5	9.3	4.0	30.4	7.6
5	22	M	W	11.7	17.5	1.5	5.7	44.4	7.8	3.6	46.0	12.8
6	22	M	W	7.9	25.3	3.2	5.7	37.3	6.5	6.9	42.8	6.2
7	41	F	C	7.3	17.4	2.4	5.7	26.4	4.6	6.1	38.0	6.2
8	24	M	W	7.7	32.7	4.2	5.2	17.5	3.4	5.3	17.5	3.3
9	23	M	W	12.4	30.2	2.4	4.4	35.3	8.0	5.1	45.1	8.8
10	23	M	W	17.2	29.5	1.7	3.5	9.2	2.6	3.5	34.8	9.9
11	22	M	W	9.2	18.4	2.0	6.9	22.3	3.2	6.6	57.3	8.7
Mean	..	..	..	10.7	28.3	2.8	5.4	31.5	5.9	5.3	39.9	8.0
Max.	..	..	..	17.7	46.7	4.8	8.7	75.6	9.4	8.3	76.8	12.9
Min.	..	..	..	7.0	17.4	1.5	3.5	8.3	1.5	3.1	10.4	1.9

C = Comfortable environmental conditions. H. & H. = Hot and humid environmental conditions. H.H.:C = Ratio of rates in hot and humid environment to that in comfortable environment.

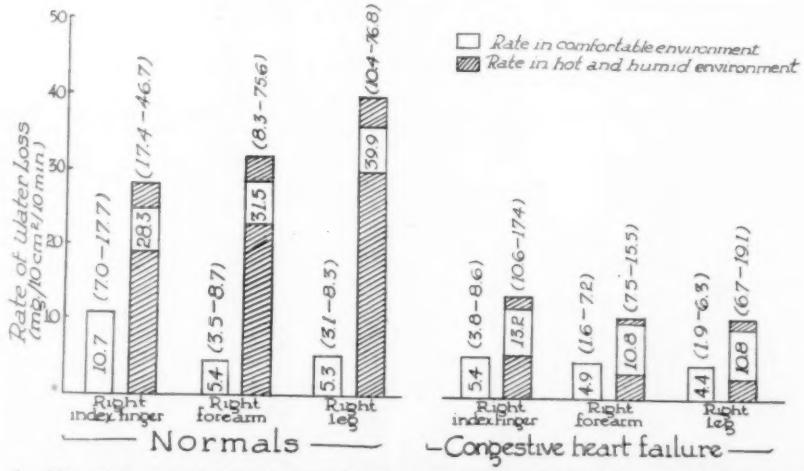

FIG. 1.—The rates of water loss in normal subjects and patients with left and right ventricular congestive heart failure (functional Class IV). The mean values are indicated in the bars and the extremes are enclosed in the parenthesis.*

* This applies for all figures.

their reaction to the two conditions of the room. With few exceptions, the subjects preferred the comfortable room conditions. There were 3 negro patients who preferred the hot and humid room conditions during the period of study and rest, although they admitted it would not be satisfactory were they at work or moving around. These 3 subjects found the temperature of 20° C. (68° F.) uncomfortably cool. All subjects with the exception of those in severe congestive heart failure, withstood the hot and humid environment fairly well, although most of them found it very uncomfortable. They complained of restlessness,

TABLE 2.—THE RATES OF WATER LOSS IN 10 PATIENTS WITH VARIOUS DISEASED STATES OTHER THAN CONGESTIVE HEART FAILURE

Subject				Parts studied									
				Finger			Forearm			Leg			
No.	Age	Sex	Color	C	H. & H.	H.H.:C	C	H. & H.	H.H.:C	C	H. & H.	H.H.:C	Diagnosis
12	53	F	C	9.4	49.5	5.3	5.1	31.6	6.2	5.3	31.9	6.0	Diab. mellitus
13	14	F	C	2.9	48.5	16.7	4.0	33.3	8.3	1.3	32.9	25.3	Subacute glom. neph.
14	45	M	W	..	..	..	5.3	9.5	1.8	5.5	9.5	1.7	Cirr. of liver; edema of legs
15	22	F	C	5.9	..	..	4.1	..	..	3.1			
16	17	M	C	5.3	13.4	2.5	5.2	17.0	3.3	5.3	11.6	2.2	F.U.O.
17	46	M	W	4.2	20.6	4.9	4.3	60.5	14.1	4.3	46.0	10.7	Pern. anemia
18	40	F	C	6.9	29.6	4.3	4.4	12.9	2.9	5.8	11.6	2.0	Diab. mellitus
19	..	F	C	13.5	57.7	4.3	3.7	36.3	9.8	3.7	46.1	12.5	PID with psychoneurosis
20	64	M	C	4.0	10.4	2.6	2.7	8.7	3.2	3.5	8.9	2.5	Senility
21	20	F	C	12.8	39.7	3.1	4.0	85.5	21.4	3.3	89.3	27.1	Ac. rheumatic fever
Mean	..	..	..	7.2	33.7	4.9	4.3	32.8	7.1	4.1	32.0	9.0	
Max.	..	..	..	13.5	57.7	16.7	5.3	85.5	21.4	5.8	89.3	27.1	
Min.	..	..	..	2.9	10.4	2.5	2.7	9.5	1.8	1.3	8.9	1.7	

C = Comfortable environmental conditions. H. & H. = Hot and humid environmental conditions. H.H.:C = Ratio of rates in hot and humid environment to that in comfortable environment.

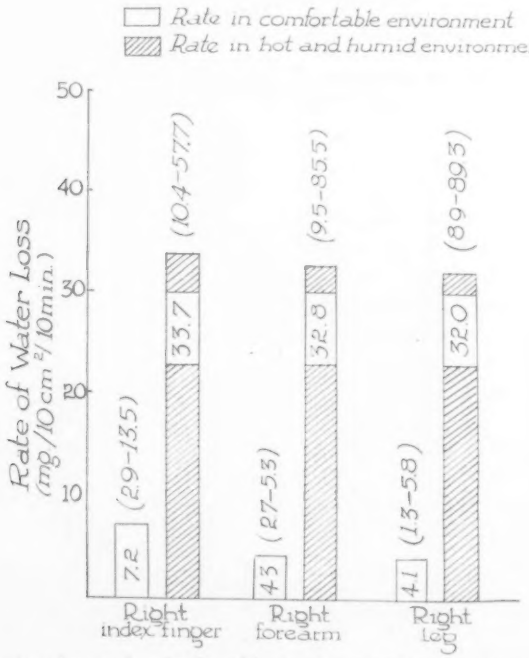

FIG. 2.—The rates of water loss in the patients with miscellaneous disease states other than congestive heart failure.

throbbing headaches, or sensations in the temporal regions, flushing of the face, a psychologic state of discomfort and unhappiness and annoyance. There was vertigo at times.

The patients with severe congestive heart failure complained most of discomfort from the hot and humid room. Three patients objected bitterly to the heat and humidity. They experienced a sense of marked suffocation and became restless, then very excited and very dyspneic, finally developing almost a state of panic. They were unable to remain in the room,

TABLE 3.—THE RATES OF WATER LOSS IN PATIENTS WITH MILD, MODERATE AND SEVERE RIGHT AND LEFT VENTRICULAR CONGESTIVE HEART FAILURE

Subject				Parts studied: Finger			Forearm			Leg			State of failure
No.	Age	Sex	Color	C	H. & H.	H.H.:C	C	H. & H.	H.H.:C	C	H. & H.	H.H.:C	
22	12	M	C	8.6	34.8	4.0	3.9	70.7	18.2	3.7	77.1	20.8	Slight to none
23	42	F	C	8.2	38.8	4.7	5.7	37.7	6.6	5.3	31.2	5.9	Slight to moderate
24	51	M	C	6.0	..	..	4.7	..	..	5.2	..	..	Slight to moderate
25	38	F	C	8.9	28.3	3.2	6.9	43.1	6.2	5.8	29.3	5.1	Slight
26	68	F	C	5.6	23.7	4.2	3.5	20.3	5.8	2.7	30.7	11.4	Slight to moderate
Mean	..	..	..	7.5	31.4	4.0	4.9	43.0	9.2	4.5	42.1	11.3	
Max.	..	..	..	8.9	38.8	4.7	6.9	70.7	18.2	5.8	77.1	20.8	
Min.	..	..	..	5.6	23.7	3.2	3.5	20.3	5.8	2.7	29.3	5.1	
27	43	F	C	11.3	20.2	1.8	7.9	36.3	4.6	9.4	23.7	2.5	Moderate
28	36	F	W	7.6	20.0	2.6	9.4	21.2	2.3	12.7	35.2	2.8	Moderate
29	42	M	C	4.6	..	..	4.4	..	..	5.0	..	..	Moderate
30	52	M	C	6.7	15.4	2.3	4.0	24.4	6.1	3.3	12.1	8.7	Moderate to severe
31	28	F	C	5.2	17.5	3.4	6.9	16.1	2.3	6.0	22.8	3.8	Moderate
32	46	M	C	7.5	15.7	2.1	4.1	21.1	5.1	4.5	27.3	6.1	Moderate
Mean	..	..	..	7.2	17.7	2.4	6.1	23.8	4.1	6.8	24.2	3.8	
Max.	..	..	..	11.3	20.2	3.4	9.4	36.3	6.1	12.7	35.2	6.1	
Min.	..	..	..	4.8	15.4	1.8	4.0	16.1	2.3	3.3	12.1	2.5	
33	65	M	C	6.0	12.2	2.0	5.2	8.8	1.7	4.5	7.9	1.8	Severe
34	51	M	C	3.8	10.6	2.8	5.2	9.3	1.8	4.1	9.9	2.4	Severe
35	53	F	C	6.2	17.4	2.8	5.7	10.0	1.8	3.6	8.9	2.5	Severe
36	62	M	W	4.2	14.0	3.3	6.0	15.5	2.6	6.3	19.1	3.0	Severe
37	67	M	C	3.8	13.3	3.5	4.7	12.8	2.7	4.4	12.5	2.8	Severe
38	30	M	C	5.4	11.9	2.2	4.0	12.0	3.0	5.7	10.0	1.8	Severe
39	60	F	C	4.4	11.5	2.6	1.6	7.5	4.7	1.9	6.7	3.5	Severe
40	43	F	C	8.1	15.1	1.9	7.2	14.0	1.9	5.1	16.4	3.2	Severe
41	52	F	C	5.1	12.6	2.5	5.7	9.6	1.7	5.1	8.8	1.7	Severe
42	53	F	C	7.0	13.1	1.9	3.3	8.0	2.4	3.6	7.5	2.1	Severe
Mean	..	..	..	5.4	13.2	2.6	4.9	10.8	2.4	4.4	10.8	2.5	
Max.	..	..	..	8.1	17.4	3.5	7.2	15.5	4.7	6.3	19.1	3.5	
Min.	..	..	..	3.8	10.6	1.9	1.6	7.5	1.7	1.9	6.7	1.7	

C = Comfortable environmental conditions. H. & H. = Hot and humid environmental conditions. H.H.:C = Ratio of rates in hot and humid environment to that in comfortable environment.

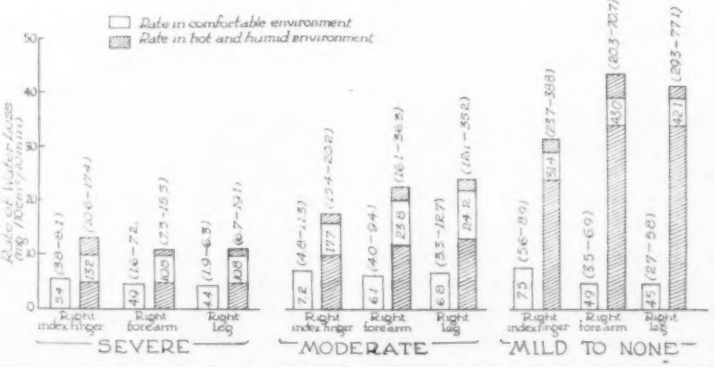

FIG. 3.—The rate of water loss in patients with various degrees of congestive heart failure. The rate of water loss in the hot and humid environment approaches normal as the heart compensates.

making it impossible to conduct the measurements. The syndrome precipitated by the hot and humid air, resembled an acute episode of cardiac asthma. Several days later, after their congestive failure had subsided, they were able to withstand the hot and humid atmosphere and the studies were completed. It was noted that this extreme and rather dramatic reaction to the hot and humid atmosphere was particularly marked if patients were suddenly wheeled into the hot room instead of being allowed to remain in bed while the room conditions were changed from a comfortable one to a hot and humid one over a period of 15 to 20 minutes.

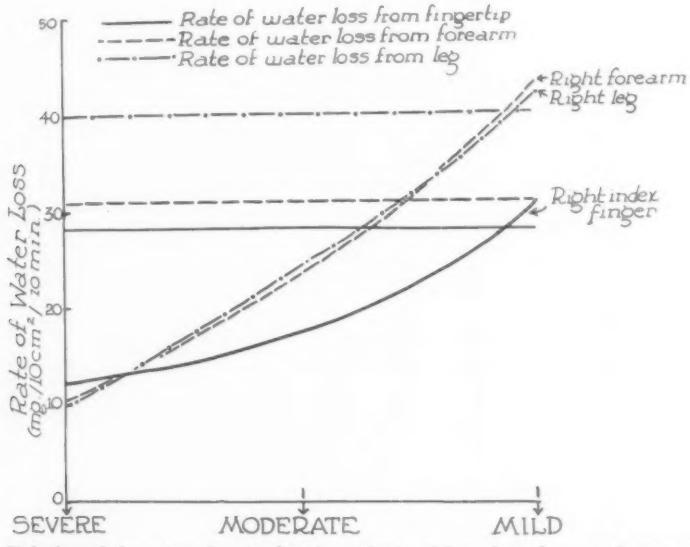

FIG. 4.—Relation of the rates of water loss in patients with various degrees of congestive heart failure to that in the normal subjects.

Under hot and humid environmental conditions, the rate of water loss from the skin of patients with severe congestive heart failure is considerably less than normal. The rate also tends to be slightly less under conditions of a comfortable environment. The mechanism for these differences is unknown. Whether or not this is a compensating mechanism designed to assist in the maintenance of a normal state of water equilibrium throughout the body during heart failure or another expression of disturbance in water distribution in heart failure is also unknown. Nevertheless, this reduction in sweating in a hot and humid atmosphere does result in an impairment in thermal regulation. Sensible perspiration is concerned mainly with emergency heat elimination whenever the thermal equilibrium is upset by rapid heat production or the conditions of the environment or the circulation interferes with heat loss by radiation, conduction, and convection. In congestive heart failure, there is an increase in heat production because of the exertion and anxiety. In addition, the impairment of the circulation with venous stasis results in impairment of heat loss by conduction, radiation and convection. The heat produced in the muscles and viscera internally cannot be efficiently transported by the blood to the surface of the body for elimination. Therefore, under such physiologic conditions heat loss by vaporization of water from the surface of the body becomes important. From the data presented, heat loss by sweating is also impaired. It is obvious, then, that patients

with congestive heart failure should be more comfortable in a cool atmosphere. This was found to be true by clinical observations. Although, because of the lack of facilities, no observations were conducted to learn the influence of the temperature and humidity of the environment upon the recuperative processes in congestive heart failure, the above acute experiments make it possible to conclude safely that a cool atmosphere is to be insisted upon in the proper management of congestive heart failure. In fact, the results make it imperative to avoid hot and humid room conditions in its treatment.

Steele and Cohn[3,9,10] attributed the fever encountered in congestive heart failure to the impairment of the circulation *per se* with a resultant impairment of heat loss by radiation, conduction and convection. This is certainly a significant factor concerned with this type of fever, particularly when the patients are in a cool and comfortable environment. As shown above, the impairment of the sweating mechanism also contributes to the abnormal elevation in body temperature in congestive heart failure. With a marked impairment of the emergency sweating mechanism, heat loss in a hot and humid atmosphere is particularly disturbed, thus predisposing even more to the accumulation of body heat.

None of the normal or diseased subjects studied, enjoyed the hot and humid atmosphere. The patients with severe congestive heart failure and impairment of sweating suffered greatest subjectively in the hot and humid atmosphere. The subjects who perspired normally suffered less. That a seizure or an acute exacerbation of congestive heart failure was or would be precipitated by a hot and humid environment is not surprising when the rôle of the cardiovascular system in heat elimination is considered. The acute demands placed upon the cardiovascular system, and the heart in particular, by an acute need for a marked increase in heat elimination may be considerable. There is a sudden increase in heart rate and cardiac output per minute with an associated diffuse vasodilatation. Such physiologic phenomena certainly exert deleterious influences on an already failing heart, resulting in an acute exacerbation of an already existing congestive heart failure or precipitating impending failure.

When dealing with a physiologic state as complicated as congestive heart failure, it is impossible under the conditions of the observations described above to evaluate the nature of the rôle of impaired sweating in the discomfort experienced by the patients with congestive heart failure. It is certainly probable that the reduced rate of heat loss by the evaporation of sweat must play a significant rôle in the patient's discomfort when in the hot, humid atmosphere.

The results of water loss in the patients with mild and moderate congestive heart failure show a return to normal of this physiologic mechanism as the cardiac function returns to normal. This is particularly well illustrated by Figure 4.

These studies indicate the great importance of considering the conditions of the environmental temperature when treating patients with congestive heart failure. This, obviously, is particularly important in subtropical and tropical climates. More attention should be given to the use of air-conditioning of hospitals. Air-conditioning of operating rooms is fairly common, but little attention is directed to air-conditioning of medical wards, especially those containing patients with congestive heart failure. The monographs on congestive heart failure contain little or nothing concerning the problem of room atmospheric conditions in the discussions of the management of congestive heart failure,[4,5,11] although a single statement by Harrison[5] ("the temperature of the room should not be allowed to become excessive during the night because heat may precipitate a seizure" [of cardiac asthma]) was encountered.

The ratios of the rates of water loss in the hot and humid environments show

that less sweating occurs for the finger tip than the limbs of the body (Tables 1 and 2). For example, in the normal the ratio for the mean rates for the tip of the finger was 2.8 (extremes 1.5 and 4.8), while for the forearm and leg the mean ratios were 5.9 (extremes 1.5 and 9.4) and 8 (extremes 1.9 and 12.9) respectively. Other data (unpublished) from this laboratory, showed that there is relatively little increase in the rate of sweating when a subject enters a hot and humid environment. These results indicate a lack of response of the sweat glands of the skin of the palms (soles as well) to a general stimulus for emergency sweating to eliminate heat by vaporization. Sweating from the palmar and plantar skin areas is, therefore, not concerned very much with heat elimination. Marked sweating initiated by psychogenic factors is well known for these areas. As indicated above, in severe congestive heart failure the sweat glands in general as well as the palmar skin fail to secrete appreciably to meet the demands of emergency heat elimination.

Summary. 1. The rate of water loss from the skin of three widely separated areas of the body (finger tip, forearm and leg), studied simultaneously, showed a marked impairment of sweating in patients with severe (Class IV) congestive heart failure resting in a hot and humid environment. Under these conditions, the mean rates of water loss varied between 27 and 47% of that in normal subjects under similar environmental conditions.

2. As the congestive heart failure subsided, the rate of water loss or sweating in hot and humid atmospheric conditions returned to normal, reaching normal rates when the failure became nil or disappeared.

3. The mean rate of water loss in a group of patients suffering from disease states other than congestive failure was normal.

4. The hot and humid room atmosphere produced more discomfort in the patients with severe congestive heart failure than in those without failure or only mild failure. In 3 instances, seizures of cardiac asthma with the associated anxiety and almost panic were precipitated by the hot and humid environment.

Conclusions. 1. The importance of ensuring a cool and comfortable atmosphere in order to avoid any unnecessary excitation of the thermal regulatory mechanism is emphasized in the therapeutic management of congestive heart failure. It is well to remember that conditions of the environment which result in a stimulation of the physiologic processes concerned with heat elimination result in an excitation of the cardiovascular mechanisms. The cardiovascular system is greatly involved in heat elimination especially when heat loss by sweating is impaired. During congestive heart failure, the cardiovascular system should have only a minimum demand placed upon it.

2. A greater need for air-conditioning in medical wards containing patients with heart disease is emphasized. This is particularly important in subtropical and tropical climates.

The author wishes to express his appreciation to Mr. G. Morgavi for his keen interest and significant technical assistance in these studies.

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THE RESPIRATORY QUOTIENT AND BLOOD PYRUVATE AND LACTATE RESPONSES AFTER ORAL INGESTION OF GLUCOSE AND FRUCTOSE IN DIABETES MELLITUS WITH AND WITHOUT INSULIN

By Howard F. Root, M.D.

Elmer Stotz, Ph.D.

and

Thorne M. Carpenter, Ph.D.

BOSTON, MASSACHUSETTS

(From the George F. Baker Clinic, Dr. Elliott P. Joslin, Medical Director, New England Deaconess Hospital, the Department of Biological Chemistry, Harvard Medical School, and the Nutrition Laboratory, Carnegie Institution of Washington)

The abnormally low respiratory quotient (R.Q.) observed in diabetes and the failure to observe a rise in R.Q. in diabetic animals and man after glucose administration as contrasted to the positive response observed in normal animals and human subjects[7,12,14] have been principal arguments for the belief that glucose is not adequately oxidized in diabetes. This evidence for "under-utilization" of sugar in diabetes has been assailed, particularly by Soskin,[15] and his comments are partially justified in that other metabolic transformations could also contribute to or account for the lowered R.Q. noted in diabetes. It was evident that another indicator of the intensity of carbohydrate oxidation was required to substantiate the interpretations of the R.Q. measurements. The carbohydrate intermediate pyruvic acid (PA) and its reduction product (LA) are readily measured in the blood, and their measurement offers a means of estimating the intensity of an intermediate stage of carbohydrate metabolism.

Perhaps the most significant recent contribution to an understanding of the biochemical defect in diabetes is the finding of a negative PA response to glucose administration. Bueding, Stein, and Wortis[3] noted an average rise in blood PA of 0.46 mg. % (from approximately 1 mg. %) at the end of 1 hour after the ingestion of 1.75 gm. of glucose per kg. of body weight. Both Bueding and coworkers[4] and Klein[13] showed however that such a response was absent in diabetic patients unless insulin was also administered. These findings were even more clearly demonstrated with depancreatized dogs[6] and have led to the conclusion that insulin is concerned in the formation of pyruvate from glucose. Chesler and Himwich[9] have shown that the ratio between PA and LA underwent only slight fluctuations as the result of injection of insulin into depancreatized dogs.

This paper presents simultaneous measurements of R.Q. with blood sugar, PA, and LA changes after the administration of 50 gm. of glucose or fructose, with or without insulin, to diabetic subjects. A negative response in R.Q. was nearly invariably accompanied by a negative response of PA and LA, but when a significant rise in R.Q. was obtained, particularly as a result of previous insulin administration, PA and LA also increased. The findings confirm earlier results on the PA response to glucose and support the contention that the negative R.Q. response to glucose in diabetes indicates a decreased oxidation of carbohydrate.

Procedure and Methods. The respiratory exchange* was measured with an open-circuit helmet apparatus[2] and gas-analysis apparatus.[8] The latter was standardized each day prior to the metabolism test by analyses of samples of outdoor air. The patient, without breakfast, came to the metabolism laboratory between 8 and 9 A.M. and lay quietly in bed for 30 minutes. The helmet was then put over the head, the patient

* The respiratory exchange measurements and the gas analyses were made by Miss Jeannette F. Rayner.

was connected with the respiration apparatus, and after a 15-minute preliminary period the basal metabolism was measured in 3 consecutive 10 minute periods. The helmet was then removed, and the patient drank the sugar solution, usually in about 1 minute. The solution consisted of 50 gm. of glucose or fructose dissolved in 300 cc. of water, and an additional 50 cc. of water was used for a rinse. The temperature of the dose ranged from 15 to 20° C. One hour after the ingestion of glucose and 30 minutes after ingestion of fructose, the metabolism measurements were continued for five 10 minute periods. These were not all consecutive but were grouped in series of 2, 2 and 1 each, with a 15 minute pause after each series during which time the helmet was removed from the patient's head.

Samples of blood were taken from the basilic vein, with care taken to remove tourniquet to avoid stasis, at the end of the basal measurements and 30, 60, 90 and 120 minutes after ingestion of the sugar. The blood samples were analyzed for blood sugar by the method of Folin,[11] PA according to Bueding and Wortis[6] and LA by the colorimetric method of Barker and Summerson.[1] Blood for PA analysis was drawn and preserved with the special precautions against loss advised by Bueding and Wortis (above).

In 26 tests with glucose and 13 tests with fructose the patients received no insulin along with the sugar and, in fact, had been without insulin for varying lengths of time prior to the tests, as indicated in the Tables. In 20 tests with glucose and 2 tests with fructose, crystalline insulin (solution of zinc insulin crystals) was given subcutaneously immediately before or after the patient drank the sugar solution. The amount given varied according to the needs of the patient.

Results. *Clinical Data.* In Tables 1 and 2 are reported the clinical data regarding the patients, including age of patient and duration of disease, information concerning the insulin treatment on the day before the metabolism test, explanatory remarks about the duration of the diabetes and any accompanying complications. The patients are divided into four main groups, those who received glucose without and with simultaneous administration of insulin, and those who received fructose without and with simultaneous administration of insulin. In these groups there are subdivisions of the patients as follows: (1) those who had not been taking insulin at all; (2) those who had not received insulin for over 24 hours, that is, who had taken no insulin on the day before the test; (3) those who had been without insulin for 24 hours, that is, who had had insulin at 7 or 8 A.M. on the day preceding the test; (4) those who had had insulin within 12 to 20 hours before the test; and (5) those who had had insulin within 1 to 2 hours before the test.

Tables 1 and 2 show that 5 patients had had the disease less than 1 year, 12 patients had had the disease 1 to 5 years, 14 patients, between 5 and 10 years, leaving 4 patients who had the disease more than 10 years. Nine patients were under 20 years of age, 22 were between 20 and 50 years of age, and 9 were over 50 years of age.

Glucose Without Insulin. In Table 3 are reported the results of the measurements on the patients who were given orally 50 gm. of glucose without simultaneous injection of insulin. Among the patients who had not been taking insulin at all or had not received insulin for over 24 hours, there are 4 (Nos. 37, 35, 4 and 8) who showed definite increases in the R.Q. above the basal level after ingestion of the glucose. Of these, 2 (Nos. 37 and 4) also showed definite increases in the PA and the LA content of the blood. No. 35 showed small increases in the PA at $1\frac{1}{2}$ and 2 hours after ingestion and a very slight increase in the LA at $1\frac{1}{2}$ hours. No. 8 had no significant increases in either PA or LA.

The group of patients who had received insulin at 7 or 8 A.M. on the day preceding the test have been divided into two subgroups, those who had a definite rise in R.Q. in all or in some of the periods following the ingestion of glucose and those who had no rise or else a fall in R.Q. after the glucose. In the first of these subgroups, all 5 patients had rises in R.Q in at least one series of periods, and 3 of

TABLE 1.—CLINICAL DATA REGARDING DIABETIC PATIENTS WHO RECEIVED 50 GRAMS OF DEXTROSE BY MOUTH

Type of test and case no.	Age of patient (yrs.)	Duration of disease	Insulin on day before test: Crystalline (units)	Insulin on day before test: Protamine zinc (units)	Time given	Remarks
			50 GRAMS OF DEXTROSE			
			Without Insulin 24 Hours Before Test			
1	28	4 yrs.	..	24	7.00 A.M.	
2	59	6 "	24	56	8.00 A.M.	Insulin resistant
3	20	3 "	250	..	6.10 A.M.	Coma on preceding day
4	26	5 mos.	0	0	...	Mild diabetes; takes no insulin
5	59	7 yrs.	8	28	8.00 A.M.	
6	48	10 "	0	0	...	Takes no insulin
7	42	4 "	24	48	7.00 A.M.	Acidosis 4 days previous
8	56	2 "	0	0	...	Thyroidectomy 2 mos. previous; takes no insulin; remission of diabetes
9	19	3 wks.				
10	16	2 "	24	48	7.00 A.M.	
11	43	10 yrs.	120	..	8.10 A.M.	
12	35	17 "	8	32	8.00 A.M.	Unstable; highly sensitive to insulin
13	13	..	..	30	..	New diabetic
			Without Insulin 12 to 20 Hours Before Test			
14	16	5 yrs.+	16	44	7.30 A.M.	Coma 4 days previous
			8	..	12.30 P.M.	
			8	..	4.30 P.M.	
15	35	8 "	10	..	4.30 P.M.	
16	47	1 yr.	24	48	8.00 A.M.	
			10	..	11.30 A.M.	
17	16	..	..	16	9.00 P.M.	New diabetic; has had insulin only once
18	26	7 yrs.	20	36	7 00 A.M.	
			10	..	12 NOON	
19	62	21 "	650	..	9.30 A.M.	Areas of fatty atrophy; insulin resistant
			550	..	12.30 P.M.	
			500	..	5.30 P.M.	
			150	..	9.00 P.M.	
20	38	7 "	60	..	6.30 A.M.	Acidosis day before test
			24	..	10.00 A.M.	
			8	..	2.00 P.M.	
			8	..	6.00 P.M.	
21	31	5 "	24	40	7.00 A.M.	Insulin resistant
			10	..	12 NOON	
			10	..	5.00 P.M.	
22	20	13 yrs.	16	..	5.00 P.M.	Dwarf; adm. to hosp. on previous day; prob. had insulin at home before admission
23	56	7 "	30	50	7.00 A.M.	Coma 5 days previous
			12	..	12 NOON	
			12	..	5.00 P.M.	
			50 GRAMS OF DEXTROSE + INSULIN			
			Without Insulin 24 Hours Before Test			
2	59	6 yrs.	20	48	8.00 A.M.	Insulin resistant
24	57	4 "	..	24	8.15 A.M.	Adenoma of thyroid
10	16	2 wks.	20	40	7.00 A.M.	
17	16	..	16	36	7.00 A.M.	
25	53	8 yrs.	6	20	8.00 A.M.	
4	26	5 mos.	0	0	...	Mild diabetes
26	52	3 yrs.	16	36	9.15 A.M.	Acidosis on 3 prec. days; possible B_1 defic. may explain rise in PA and LA of blood
27	17	2 "	50	50	7.00 A.M.	
28	72	3 "	12	44	7.00 A.M.	Coma 10 days before test
			Without Insulin 15 to 20 Hours Before Test			
29	31	...	20	40	1.30 P.M.	Coma on preceding day
22	20	13 yrs.	18	48	7.00 A.M.	
			6	..	12 NOON	
			4	..	5.00 P.M.	
3	20	3 "	26	50	7.00 A.M.	Coma 6 days before
			8	..	5.00 P.M.	
30	47	11 "	..	24	12.30 P.M.	Pituitary tumor and hypopituitarism
19	62	21 "	600	..	8.30 A.M.	Insulin resistant
			500	..	12.30 P.M.	
			450	..	3.30 P.M.	
11	43	10 "	120	..	12.30 P.M.	Insulin resistant
			40	..	5.00 P.M.	
31	45	2 mos.	18	36	7.30 A.M.	
			6	..	12 NOON	
20	38	7 yrs.	30	36	7.00 A.M.	Acidosis 9 days previous
			6	..	5.00 P.M.	
32	27	6 "	..	8	7.30 A.M.	
			10	..	12 NOON	
			10	..	5.00 P.M.	
			No Insulin Taken on Day Before Test			
33	15	1 mo.	0	0	...	Goiter; insulin reaction after test
34	40	9 yrs.	0	0		
35	47	1 yr.+	0	0		
36	34	2 yrs.	0	0		
			50 GRAMS OF DEXTROSE			
			Takes No Insulin			
37	17	...	0	0	...	Diabetes and renal glycosuria

TABLE 2.—CLINICAL DATA REGARDING DIABETIC PATIENTS WHO RECEIVED 50 GRAMS OF FRUCTOSE

Type of test and case no.	Age of patient (yrs.)	Duration of disease	Insulin on day before test: Crystalline (units)	Insulin on day before test: Protamine zinc (units)	Insulin on day before test: Time given	Remarks
50 GRAMS OF FRUCTOSE						
Without Insulin 24 Hours Before Test						
15	35	8 yrs.	20	66	8.30 A.M.	
36	34	2 "	6	24	7.00 A.M.	New diabetic
30	47	11 "	6	28	7.00 A.M.	Pituitary tumor; has taken 6 gr. thyroid extract for past 3 days
7	42	4 "	24	56	7.00 A.M.	Coma 6 days previous; took cup of black coffee before test
Without Insulin 12 to 20 Hours Before Test						
1	28	4 yrs.	..	20	12.30 P.M.	
35	47	1 yr.+	..	20	12.30 P.M.	
38	49	6 yrs.	14	30	8.00 A.M.	
			4	..	4.30 P.M.	
13	13	..	16	32	12.30 P.M.	
			4	..	5.00 P.M.	
12	35	17 yrs.	12	28	8.00 A.M.	Unstable; highly sensitive to insulin
			8	..	4.30 P.M.	
Insulin 1 to 2 Hours Before Test						
14	16	5 yrs.+	20	50	7.15 A.M.	Coma 6 days previous
			4	..	12 NOON	
21	31	5 "	50	80	7.00 A.M.	Insulin resistant
			6	..	12 NOON	
16	47	1 yr.	24	48	12 NOON	
			8	..	4.30 P.M.	
39	18	7 yrs.	20	44	7.00 A.M.	
			6	..	12 NOON	
			6	..	5.00 P.M.	
50 GRAMS OF FRUCTOSE + INSULIN						
29	31	..	20	40	12 NOON	Coma 2 days previous
			10	..	5.00 P.M.	
25	53	8 yrs.	..	20	8.00 A.M.	

TABLE 3.—CHANGES FROM BASE-LINE IN RESPIRATORY QUOTIENT, AND SUGAR, PYRUVIC ACID AND LACTIC ACID OF BLOOD OF DIABETIC PATIENTS AFTER INGESTION OF 50 GRAMS OF DEXTROSE

Condition and case no.	Respiratory quotient: Basal	Respiratory quotient: Changes from basal after dextrose: 1–1½ hrs.	Respiratory quotient: Changes from basal after dextrose: 1½–2 hrs.	Respiratory quotient: Changes from basal after dextrose: 2–2½ hrs.	Blood sugar (mg. per 100 cc.): Basal	Blood sugar: Changes from basal after dextrose: ½ hr.	Blood sugar: Changes from basal after dextrose: 1½ hrs.	Blood sugar: Changes from basal after dextrose: 2 hrs.	Pyruvic acid (mg. per 100 cc.): Basal	Pyruvic acid: Changes from basal after dextrose: ½ hr.	Pyruvic acid: Changes from basal after dextrose: 1½ hrs.	Pyruvic acid: Changes from basal after dextrose: 2 hrs.	Lactic acid (mg. per 100 cc.): Basal	Lactic acid: Changes from basal after dextrose: ½ hr.	Lactic acid: Changes from basal after dextrose: 1½ hrs.	Lactic acid: Changes from basal after dextrose: 2 hrs.
TAKES NO INSULIN (MILD OR BORDERLINE DIABETES)																
37	0.81	+0.09	+0.09	+0.12	62	+ 54	+ 12	+ 27	1.4	+0.2	+0.4	+0.2	8.8	+1.6	+4.0	+3.7
4	0.82	+0.03	+0.06	+0.04	112	+ 63	+123	+144	1.5	+0.4	+0.6	+0.3	12.2	+4.2	+6.6	+4.1
6	0.88	0.00	+0.01	+0.01	54	+ 51	+ 72	+107	1.3	+0.1	+0.1	+0.1	6.4	+0.2	+0.2	−0.2
8	0.84	+0.11	+0.09	+0.03	106	+ 34	+ 81	+ 14	1.4	0.0	0.0	0.0	8.8	+0.2	+0.3	+0.3
NO INSULIN TAKEN ON DAY BEFORE TEST																
35	0.77	+0.05	+0.07	+0.04	122	+ 95	+145	+113	1.0	0.0	+0.2	+0.2	7.0	+0.2	+0.6	+0.2
36	0.82	−0.01	−0.01	−0.01	89	+ 43	+167	+189	1.0	+0.1	0.0	0.0	6.2	+0.4	+0.2	+0.2
WITHOUT INSULIN 24 HOURS BEFORE TEST																
1	0.81	+0.01	+0.03	+0.01	77	+ 33	+ 82	..*	1.2	0.0	0.0	..*	6.7	0.0	0.0	*
2	0.77	+0.02	+0.02	+0.05	163	+ 57	+111	+104	1.3	0.0	+0.1	0.0	8.0	0.0	+0.1	0.0
3	0.75	0.0	+0.03	+0.04	70	+ 17	+130	+147	1.1	0.0	0.0	−0.1				
5	0.82	+0.07	+0.07	+0.11	157	+ 32	+133	+146	1.3	0.0	+0.2	+0.3	8.8	+0.4	+1.8	+2.7
7	0.80	+0.04	+0.06	+0.05	177	+ 90	..	+187	1.2	+0.1	+0.1	+0.1	6.8	+0.1	+0.1	−0.1
10	0.89	−0.02	−0.03	−0.01	59	+ 1	+ 32	+ 85	1.2	0.0	0.0	+0.1	6.4	0.0	+0.1	+0.2
9	0.84	−0.03	−0.03	−0.04	87	+ 16	+103	+130	1.3	0.0	+0.2	+0.2	8.6	−0.1	+2.3	+2.4
13	0.80	−0.01	−0.02	−0.01	151	+ 36	+105	+148	1.2	+0.1	0.0	+0.1	8.7	+0.7	+0.3	+0.3
11	0.79	0.00	−0.01	+0.02	274	+ 59	+142	+170	1.0	−0.1	−0.1	−0.2	7.5	−0.9	−1.6	−1.6
12	0.76	0.00	−0.03	−0.04	206	+102	+182	+132	1.5	0.0	+0.1	0.0	9.2	0.0	+0.2	0.0
WITHOUT INSULIN 12 TO 20 HOURS BEFORE TEST																
14	0.85	+0.01	−0.03	+0.05	160	+114	+198	+210	1.2	+0.1	0.0	0.0	8.6	+1.4	+0.3	+0.3
15	0.72	+0.04	+0.07	+0.05	215	+ 18	+155	+149	1.3	0.0	−0.1	0.0	9.6	+0.3	−0.4	−0.2
16	0.79	+0.03	+0.02	+0.01	256	+ 47	+124	+144	1.3	0.0	0.0	0.0	9.0	0.0	+0.1	+0.1
17	0.74	+0.02	+0.03	+0.02	267	+ 97	+177	+ 93	2.2	−0.2	+0.1	0.0	13.2	−2.2	−0.2	−0.5
18	0.74	+0.02	+0.09	+0.10	220	+ 1	+ 21	+ 24	1.2	+0.1	+0.3	+0.5	6.8	+0.6	+2.6	+3.5
19	0.77	+0.02	+0.03	..	111	+175	+247	+222	1.2	0.0	0.0	0.0				
20	0.74	+0.05	+0.04	+0.03	57	+187	+ 50	+141	1.1	0.0	0.0	0.0	6.8	0.0	−0.1	+0.1
21	0.74	−0.01	−0.02	0.00	196	+ 31	+ 98	+ 12	1.4	0.0	+0.1	0.0	8.8	+0.2	+0.8	+0.4
22	0.77	−0.02	−0.01	−0.01	145	+ 72	+178	+193	1.4	−0.2	−0.1	−0.1	8.6	−0.6	−0.2	−0.2
23	0.77	−0.02	−0.02	..	175	+ 78	+107	+ 92	1.3	0.0	+0.1	−0.1	10.6	0.0	−0.1	−0.4

* The changes in the blood values 2½ hrs. after dextrose were +105, 0.0 and +0.1 respectively.

them (Nos. 2, 5 and 7) had definite rises in R.Q. in all the measurements. However, there were significant rises in PA and LA with only one of these patients (No. 5), at 1½ and 2 hours after ingestion of glucose. This patient also had the most marked rises in R.Q. From the data for this subgroup it can be concluded that increases in R.Q. after glucose may amount to 0.06 without any significant change in either PA or LA of the blood. In the other subgroup, that is, patients who showed either a fall in R.Q. or no marked change, there were significant increases in PA and LA at 1½ and 2 hours with No. 9. The only explanation that can be given for this fall in R.Q. accompanied by increases in the blood acids is that the basal R.Q. may have been too high because of nervous apprehension during the basal period and hence the true changes in R.Q. are not shown. The remainder of the data for this subgroup are consistent in that, with no rise or a fall in R.Q., there was no significant rise or else a fall in the PA and LA of the blood.

The group of patients who had not received insulin within 12 to 20 hours before the tests were made is also divided into subgroups, that is, those who showed a definite rise in R.Q. at some period after the ingestion of glucose and those who did not. In the first subgroup there are 2 patients (Nos. 15 and 20) who had definite rises in R.Q. in all the periods after glucose and yet showed no increase in either PA or LA in any of the blood samples. The rises in R.Q. of No. 15 are of such an order of magnitude that one would expect a rise in PA and LA if there is a relationship between changes in R.Q. and changes in these acids, and yet the rises in the blood acids are only slight. The first R.Q. of No. 20 after glucose also underwent a marked rise. With No. 18 there was a marked rise in R.Q. and PA and LA at 1½ to 2 hours and at 2 to 2½ hours. In none of the other periods were there any significant increases in either PA or LA when there were rises in R.Q. None of the rises in R.Q. except those already noted were large. In the second subgroup the data are thoroughly consistent in that with no rise or a fall in R.Q. there was no increase in the PA and LA of the blood.

Practically none who had had coma or acidosis recently or were classified as insulin resistant gave any marked rises in R.Q., PA, and LA.

In general, patients with diabetes may show slight rises in R.Q. after ingestion of 50 gm. of glucose without significant increases in the PA and LA of the blood, but when the rises in R.Q. are over 0.05, these are likely to be accompanied by significant increases in the PA and the LA of the blood.

Glucose With Simultaneous Injection of Insulin. Twenty patients were given 50 gm. of glucose together with subcutaneous injection of insulin in various amounts. The results of the measurements are shown in Table 4.

The 3 patients to whom no insulin was given on the day before the tests all showed definite rises in R.Q. The rises with Nos. 31 and 34 were somewhat larger than would be obtained if normal persons were given glucose alone, so that insulin brought about a larger increase in R.Q. than normally occurs. The insulin dosage was large enough so that there was a marked fall in the blood sugar with 2 patients instead of a rise that might occur after glucose alone. One patient (No. 33) had definite increases in the PA and LA at all 3 times of measurement. No. 34 gave a rise in PA and LA at 1½ and 2 hours after glucose. The third patient (No. 4) had a significant rise only in the LA, at 1½ and 2 hours.

Of the patients to whom insulin was given at 7 or 8 A.M. on the day preceding the test, all showed rises in R.Q. in all the periods except the first with No. 27. The rises in R.Q. with Nos. 28, 10 and 26, were large and greater than would occur, on the average, in normals with glucose alone. These 3 patients also showed increases in both PA and LA at 1½ and 2 hours. With the exception of Nos. 27 and 24, all patients showed rises in LA at 1½ and 2

23	. . . .	0.77	−0.02	−0.02	..	175	+ 78	+107	+ 92	1.3								

* The changes in the blood values 2½ hrs. after dextrose were +105, 0.0 and +0.1 respectively.

hours, and the same is true for the most part with PA.

Of the patients who received no insulin within 15 to 20 hours before the tests, 3 (Nos. 31, 20 and 32) had marked rises in R.Q., particularly in the second and third periods, and the rises were accompanied by rises in PA and LA. With Nos. 22 and 3 there were small or no rises in R.Q., PA, and LA. No. 30 had large rises in R.Q. but little or no rise in the acids until the 2 hour period.

followed by large rises in R.Q., indeed much larger in some patients than would occur normally with healthy persons after glucose alone. In many instances there were large increases in both PA and LA, particularly in the latter. The increases in LA were with some patients larger than with normals after 100 gm. of glucose. Edwards and others[10] found that with normal men ingestion of 100 gm. of glucose caused an increase in LA of 3 to 4 mg. per 100 cc. of blood at 45 minutes after

TABLE 4.—CHANGES FROM BASE-LINE IN RESPIRATORY QUOTIENT AND SUGAR, PYRUVIC ACID AND LACTIC ACID OF BLOOD OF DIABETIC PATIENTS AFTER INGESTION OF 50 GRAMS OF DEXTROSE AND SIMULTANEOUS ADMINISTRATION OF INSULIN

		Respiratory quotient				Blood sugar (mg. per 100 cc.)				Pyruvic acid (mg. per 100 cc.)				Lactic acid (mg. per 100 cc.)			
			Changes from basal after dextrose and insulin				Changes from basal after dextrose and insulin				Changes from basal after dextrose and insulin				Changes from basal after dextrose and insulin		
Condition and case no.	Insulin (un.)	Basal	1-1½ hrs.	1½-2 hrs.	2-2½ hrs.	Basal	½ hr.	1½ hrs.	2 hrs.	Basal	½ hr.	1½ hrs.	2 hrs.	Basal	½ hr.	1½ hrs.	2 hrs.
No Insulin Taken on Day Before Test																	
33	20	0.73	+0.13	+0.13	+0.21	183	− 35	− 40	−121	1.7	+0.2	+0.3	+0.6	8.8	+1.4	+ 5.7	+ 8.2
34	20	0.71	+0.16	+0.18	+0.16	364	− 10	− 36	− 78	1.5	+0.1	+1.2	+1.3	10.4	+0.4	+ 8.4	+ 8.6
4	10	0.82	+0.05	+0.07	+0.05	108	+ 29	+ 39	− 25	1.4	0.0	+0.1	+0.1	8.6	0.0	+ 2.8	+ 3.2
Without Insulin for 24 Hours Before Test																	
27	20	0.82	0.00	+0.03	+0.04	127	+ 95	+111	+ 88	1.2	−0.2	−0.2	−0.1	5.4	−0.4	− 0.1	− 0.1
28	24	0.79	+0.08	+0.13	+0.10	112	+ 90	+103	+ 99	1.2	+0.1	+0.4	+0.5	8.7	+0.5	+ 3.0	+ 3.7
2	30	0.79	+0.06	+0.05	+0.05	182	+ 71	+ 92	+ 68	1.5	0.0	+0.5	+0.4	8.3	+0.5	+ 2.9	+ 2.7
24	10	0.81	+0.05	+0.07	+0.07	119	+ 38	+125	+108	1.2	0.0	..	+0.1	6.6	+0.2	..	+ 0.3
10	20	0.94	+0.09	+0.10	+0.12	65	− 12	− 17	− 33*	1.2	+0.1	+0.2	+0.1*	6.5	+0.4	+ 1.6*	+ 1.5*
17	20	0.82	+0.06	+0.07	+0.07	126	+ 63	+109	+ 41	1.7	+0.1	+0.6	+0.7	10.5	+1.8	+ 8.5	+ 7.5
25	20	0.84	+0.10	..	..	44	+ 13	+ 24	..	1.5	−0.1	+0.1	..	11.2	−2.0	+ 0.4	
26	20	0.79	+0.20	+0.16	+0.08	256	+ 22	+ 52	+ 14	0.7	0.0	+2.1	+2.2	3.8	+0.3	+19.9	+21.5
Without Insulin 15 to 20 Hours Before Test																	
29	20	0.76	+0.03	+0.04	+0.02	199	+ 79	+113	+118	1.2	0.0	+0.6	+0.5	8.8	+0.2	+ 5.6	+ 5.8
22	20	0.80	0.0	+0.01	+0.03	105	+120	+162	+122	1.1	+0.1	+0.1	+0.2	6.9	+0.2	+ 0.5	+ 2.0
3	20	0.83	−0.01	+0.01	+0.04	103	+ 9	+ 89	+147	1.0	0.0	0.0	0.0	6.0	0.0	+ 0.1	0.0
30	16	0.78	+0.08	+0.09	+0.10	42	+ 37	+112	+103	1.4	+0.1	+0.1	+0.3	8.8	+0.5	+ 0.5	+ 1.9
19	300	0.77	+0.02	+0.13	...	80	+248†	...	+320	1.2	+1.1†	...	+0.3	6.8	+3.4†	..	+ 3.7
11	75	0.82	+0.01	+0.05	..	120	+ 78	+203	+210	1.1	−0.1	0.0	+0.2	7.0	−0.6	+ 1.3	+ 1.8
31	20	0.74	+0.18	+0.18	+0.18	127	+ 84	+ 93	+ 25	0.9	0.0	+0.7	+0.7	5.4	0.0	+ 5.3	+ 5.4
20	20	0.78	+0.06	+0.08	+0.12	112	+ 11	+ 31	+ 28	1.2	+0.1	+0.2	+0.3	8.0	+1.0	+ 1.8	+ 2.4
32	20	0.77	+0.05	+0.09	+0.10	129	+127	+147	+ 93	1.2	+0.2	+0.4	+0.5	7.4	+1.3	+ 3.6	+ 4.7

* The changes in the blood value 2½ hrs. after dextrose and insulin were −49, +0.2 and +2.5 mg. respectively. These values were obtained after the patient had had an insulin reaction.

† 67 minutes after dextrose and insulin.

Among the patients in Table 4, who had had recent coma or acidosis or were insulin resistant, 3 (Nos. 28, 26 and 20) gave marked rises in R.Q. All but No. 3 showed slight rises in PA and similarly all but No. 3 showed significant rises in LA even when the rise in R.Q. was low (0.06 or less).

In general, the ingestion of glucose and the simultaneous injection of insulin were

ingestion and of 1 to 3 mg. at 90 minutes. The effect of simultaneous injection of insulin along with oral ingestion of glucose is to bring about a larger increase in R.Q. in some patients than would occur in normals after glucose alone, a greater increase in LA than with normals, and a marked increase in PA at 1½ and 2 hours after ingestion. Therefore, part of the rise in R.Q. after insulin must be ascribed to

the effects of LA and PA in displacing carbon dioxide from the blood. Hence not all the rise in R.Q. can be ascribed to increased combustion of sugar, particularly when these rises are very large, but the largest effect of the acids would probably not be more than 0.03 to 0.04 on the R.Q.

In the group without insulin for 12 to 20 hours before the tests, patients Nos. 35 and 12 had large rises in R.Q. accompanied by definite increases in PA and LA, particularly No. 35. Patients Nos. 1 and 38 had little or no rise in R.Q. but did have significant increases in PA and LA. No. 13 had slight rises in R.Q. and significant

TABLE 5.—CHANGES FROM BASE-LINE IN RESPIRATORY QUOTIENT AND SUGAR, PYRUVIC ACID AND LACTIC ACID OF BLOOD OF DIABETIC PATIENTS AFTER INGESTION OF 50 GRAMS OF FRUCTOSE

Condition and case no.	Respiratory quotient: Basal	Respiratory quotient: Change from basal after fructose ½–1 hr.	1–1½ hrs.	1½–2 hrs.	Blood sugar (mg. per 100 cc.): Basal	Blood sugar: Change from basal after fructose ½ hr.	1 hr.	2 hrs.	Pyruvic acid (mg. per 100 cc.): Basal	Pyruvic acid: Change from basal after fructose ½ hr.	1 hr.	2 hrs.	Lactic acid (mg. per 100 cc.): Basal	Lactic acid: Change from basal after fructose ½ hr.	1 hr.	2 hrs.
WITHOUT INSULIN FOR 24 HOURS BEFORE TEST																
15	0.81	+0.07	+0.12	+0.08	43	+63	+ 26	+ 58	1.3	0.0	+0.6	+0.8	9.0	0.0	+ 7.3	+ 8.2
36	0.82	+0.02	−0.01	−0.02	70	..	+ 71*	+ 72	1.2	..	0.0*	+0.1	6.6	..	0.0*	+ 0.2
30	0.80	+0.04	+0.01	−0.01	274	+49	+ 90	+134	1.3	0.0	+0.7	+0.1	8.6	+ 0.4	+ 7.1	+ 1.6
7†	0.75	+0.24	+0.21	+0.05	51	+22	+ 36	+ 26	1.2	+0.7	+1.1	+0.9	8.0	+ 7.2	+12.0	+10.7
WITHOUT INSULIN FOR 12 TO 20 HOURS BEFORE TEST																
1	0.80	+0.02	+0.06	−0.04	133	+63	+ 28	+ 78	1.2	0.0	+0.8	+0.3	8.6	+ 0.4	+ 9.1	+ 1.3
35	0.81	+0.11	+0.12	+0.05	91	+40	+ 66	+ 76	1.1	+1.6	+1.5	+0.8	8.3	+13.3	+12.7	+ 7.7
38	0.84	+0.06	+0.02	−0.01	104	+ 4	+ 39	+ 48	1.2	+0.2	+0.5	+0.4	9.2	+ 2.2	+ 5.2	+ 4.8
13	0.74	+0.03	+0.03	+0.03	108	+72	+100	+127	1.2	+0.4	+0.1	0.0	6.7	+ 5.0	+ 1.3	+ 0.3
12	0.75	+0.18	+0.21	+0.05	119	+ 5	+ 56	+ 55	1.3	+0.3	+0.5	+0.8	9.0	+ 3.8	+ 4.6	+ 9.1
INSULIN 1 TO 2 HOURS BEFORE TEST																
14	0.87	+0.10	+0.12	+0.08	53	+ 6	+ 18	+ 17	1.3	+0.6	+0.4	+0.2	10.0	+ 6.6	+ 6.3	+ 4.5
21	0.76	+0.05	+0.12	+0.04	233	+31	+ 2	− 8	1.3	+0.6	+0.8	+0.4	7.4	+ 6.6	+12.2	+ 5.6
16	0.75	+0.09	+0.15	+0.02	140	+24	+ 56	− 11	1.2	+0.4	+0.8	+0.6	7.0	+ 3.0	+ 9.2	+ 7.4
39	0.79	+0.02	−0.05	−0.04	267	−11	+ 56	+ 66	1.2	+0.3	+0.7	+0.2	8.8	+ 2.6	+ 7.1	+ 2.4
20 UNITS INSULIN WITH FRUCTOSE																
29	0.73	+0.16	+0.23	+0.09	76	..	+ 81	+ 35	1.2	..	+0.3	+1.3	9.0	..	+ 2.6	+13.1
25	0.77	+0.08	+0.13	+0.09	244	..	+ 26‡	− 57	1.2	..	+0.1	+0.8	7.9	..	+ 0.6	+ 9.8

* The changes in the blood values 1½ hours after fructose were +76, 0.0 and +0.2 mg. respectively.
† Patient had a cup of black coffee before test.
‡ The changes in the blood values 1½ hours after fructose were 0, +1 and +11.1 mg. respectively.

Fructose Without and With Simultaneous Injection of Insulin. The results of the measurements on patients to whom fructose was given orally are shown in Table 5.

Of the patients without insulin since the morning of the preceding day, 2 (Nos. 15 and 7) had marked rises in R.Q. in all periods and significant increases in PA and LA in either 2 or 3 determinations. Two patients (Nos. 36 and 30) had little or no rise in R.Q. but did have some increases in PA and LA. These 2 patients form exceptions to the general rule that the ingestion of fructose by diabetic patients is accompanied by marked rises in R.Q.

rises in PA and LA. In general, with this group there was a greater rise in PA and LA with small rises in R.Q. than occurred in similar tests with glucose.

In the group with insulin 1 to 2 hours before ingestion of the fructose, 3 patients (Nos. 14, 21 and 16) had marked rises in R.Q. in at least 2 periods, accompanied by large increases in PA and LA. One patient (No. 39) had no significant rise in R.Q. and even a fall in 2 periods, but in spite of this there were definite increases in PA and LA at all 3 periods of measurement.

The 2 patients to whom insulin was given along with the fructose had large

increases in R.Q. and increases in PA and LA, particularly at the 2 hour measurement. Patients Nos. 25 and 29 showed much greater rises in R.Q., PA and LA with fructose and insulin than with glucose and insulin and patient No. 12, to whom no insulin was given with either sugar, showed very marked rises with fructose and none with glucose. One might postulate that fructose is converted to fat more readily in the diabetic than is glucose.

Two of the patients in Table 5 (Nos. 7 and 14) who had coma within 1 week showed rises in R.Q., PA, and LA and the other one (No. 39), significant rises in PA and LA. Patient No. 21 who was insulin resistant gave large rises in R.Q. and LA and a significant rise in PA. Only 4 out of 15 patients showed no definite rise in R.Q. after fructose.

In general, with diabetic patients the ingestion of fructose is more likely to be accompanied by rises in the PA and LA of the blood, even when the rise in R.Q. is small or does not take place, and these increases are more prominent at the ½ hour measurement than is the case after ingestion of glucose, particularly when the patients have received insulin 24 hours or less before the tests were made. Edwards and co-authors[10] found that at 45 minutes after ingestion of 100 gm. of fructose normal men had increases in LA of from 7.5 to 12.7 mg. per 100 cc. of blood and that similar increases occurred at 90 minutes. The corrections in the R.Q.'s of their subjects at 45 minutes, based on changes in LA and slight changes in alveolar air, amounted to from −0.07 to −0.15. However in the diabetics of this series, the increases in LA and PA were seldom of such magnitude. The maximum R.Q. after fructose tends to occur slightly later with diabetic patients than with normal persons. Undoubtedly some of the large increases in R.Q. with diabetic patients are due to the displacement of the carbon dioxide of the blood by the LA and PA, but in general with diabetic patients the increases in R.Q. after fructose are greater than those after glucose. The metabolism of fructose appears to be different from that of glucose in diabetic patients as well as in normal persons.[10]

These studies contribute to the "under-oxidation" theory of diabetes and show that the action of insulin is to promote the formation of PA, an intermediate which leads to oxidation. The increase in oxidation is very definitely shown in the greater rises in R.Q. when insulin is given with the sugars.

Summary. The respiratory quotient (R.Q.), the blood sugar, and the pyruvate (PA) and lactate (LA) levels of the blood were determined in diabetic patients before and after the oral ingestion of 50 gm. of glucose or fructose.

In a group of 26 patients who had been without insulin for varying lengths of time preceding the tests, slight rises in R.Q. after ingestion of glucose were not generally accompanied by rises in PA and LA, but when the rise in R.Q. was 0.05 or over, there was usually a rise in either PA or LA or both. With one exception, when there was no rise in R.Q. there were no significant changes in the acid levels of the blood.

In a group of 20 patients, when insulin was given immediately preceding or immediately following the ingestion of glucose, the majority showed rises in the R.Q. and acid levels of the blood, and these changes were in some patients larger than would occur with the majority of normal subjects. Insulin resistant cases required large amounts of insulin to produce a rise in R.Q. after administration of glucose. The rises in R.Q. could have been due only partially to the displacement of carbon dioxide from the blood by the organic acids.

The ingestion of 50 gm. of fructose by 15 patients produced a rise in R.Q. in 10 of them, and in all of them the PA and LA levels were increased even when no rise in R.Q. took place. In only 2 patients was the ingestion of fructose accompanied by simultaneous injection of insulin. The

rises in R.Q. and organic acid levels of the blood were, in general, larger than after the same amount of glucose. The intermediary metabolism of fructose is, with diabetic patients as with normal subjects, different from that of glucose.

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HUMAN UTILIZATION OF BIOTIN FROM VARIOUS DIETS*†

By Josephine Gardner
Helen T. Parsons
and
William H. Peterson
Madison, Wisconsin
(From the Departments of Home Economics and Biochemistry, University of Wisconsin)

The importance of biotin in the nutrition of man and animals has received considerable attention recently. Findlay and Stern[2] first suggested that a dermal and nervous syndrome of childhood called Swift's disease or pink disease showed a similarity to manifestations in rats fed a diet high in uncooked egg white. György mentioned several times the possible rôle in the prevention of human disease of the anti-egg white injury factor, called vitamin H by György.[4,5,6] An induced deficiency of biotin was brought about by including uncooked egg white in the diet of a group of men and was cured by a biotin concentrate (Sydenstricker, *et al.*[18]). The relation of biotin to certain pathologic states is still unsettled. A reduction in incidence of malaria in chickens and ducks when an adequate amount of biotin was present in the diet was demonstrated by Trager.[19] West and Woglom[20] reported that the biotin of tumor tissue was sometimes higher than that of normal tissues. Oppel[13] found little difference in the total urinary biotin of normal individuals and those with a variety of diseases. The urinary excretion of biotin of normal persons varied from 14 to 111 μg. per 24 hours and the daily fecal output varied from 86 to 191 μg. Biotin output in the urine and feces was 3 to 6 times as great as the intake from the diet (35 to 60 μg. per day), indicating synthesis of biotin, probably by intestinal microörganisms.

Little is known concerning the utilization by human beings of biotin from different sources. The balance between biotin intake and output during the consumption of a milk diet was recently reported from this laboratory (Gardner *et al.*[3]). The present paper reports four balance studies comparing the utilization by college women of biotin from diets containing different amounts of baker's yeast and beef liver. The human utilization of thiamine and riboflavin on two of these four diets has been reported elsewhere (Parsons and Collord[14]) and the utilization of biotin of these two diets has been presented in part (Parsons *et al.*[15]).

Experimental. *Subjects.* In the 4 metabolism studies presented, uniform weighed diets were consumed by a total of 15 healthy and reliable young women, 19–25 years of age. There were 4, 6, 2 and 3 subjects on Studies 1 through 4, respectively.

Diets. A uniform diet of moderate biotin content was supplemented daily with fresh baker's yeast (3, 4 or 7½ cakes weighing approximately 12 gm. each) or beef liver (77 or 185 gm. raw). The experimental Studies 1 through 4 as given in Table 2 lasted 13 to 15, 22, 8 and 18 days.

The original basal diet was planned for the study of the human metabolism of certain B vitamins in yeast. The diets in Studies 1 and 2 (Table 1) were those described by Parsons and Collord.[14] The various diets differed only in minor details according to the preference of the members of the squad. The amount of grape jelly, butter, and mayonnaise, as well as the amount and kind of bread was adjusted. Potato was substituted for squash in the studies following Study 1. The diet in Studies 3 and 4 contained less milk in order that a greater proportion of the biotin intake would be derived from bakers' yeast or beef

* Published with the approval of the Director of The Wisconsin Agricultural Experiment Station.
† This study was supported, in part, by a grant from The Nutrition Foundation, Inc.

liver. Pudding or bananas replaced ice cream for the same reason.

Since the basal diet was low in thiamine, 1 mg. per person was added daily during Study 1 and during the basal periods when no yeast or liver was consumed during Studies 2, 3 and 4.

The sequence and length of periods, the number of subjects and the supplements in the four studies are shown in Table 2.

During Studies 1 and 4, one-third of the yeast was eaten with each meal; during the second study 2 cakes were eaten with noon lunch and 1 with each of the other meals.

Methods. Twenty-four hour urinary collections were made in brown glass bottles containing 3 ml. of glacial acetic acid and 1 ml. of chloroform and were preserved with a layer of toluene. The urine was assayed for biotin after dilution. In some cases

TABLE 1.—COMPOSITION OF DIETS

		Basal diet			
		Plus raw or boiled yeast (Study 1)	Plus yeast treated 3 ways (Study 2)	Plus beef or liver (Study 3)	Plus yeast or liver (Study 4)
Breakfast:					
grapefruit juice	Gm.	200	200	150	150
bread, white	"	44	43	44	44
butter	"	10	12	10	12
grape jelly	"	30	15	10	
coffee, *ad lib.*					
Lunch:					
cheese sandwiches					
cheese, cheddar	"	55	55	50	60
bread, white	"	44	60		
bread, whole wheat	"	..	..	60	60
butter	"	10	15	20	15
lettuce	"	60	60	60	60
mayonnaise	"	..	10	15	10
apple	"	150	150	150	150
whipped cream	"	15			
sugar	"	2			
milk	"	240	240	200	200
Dinner:					
tomato juice	"	200	200		
lean beef, ground	"	150	100	180	150
cabbage	"	30	30	50	50
squash	"	100			
bread, white	"	22	22	16	16
butter	"	10	15	15	15
ice cream, vanilla	"	100	50		
ice cream, chocolate	"	..	50		
potato	"	..	100	150	125
pudding, cornstarch	"	..	..	100	
bananas	"	..	..	50	100
liver or beef	"	..	..	185*	77*
biotin content of liver	μg.	..	..	140	86
yeast, bakers', number of cakes		3†	4†	..	7.5†
biotin content of yeast	"	24	34	..	57
milk	Gm.	240			
Biotin content of basal diet	μg.	21	35	21	36

* Beef liver replaced ground beef during Period III, Study 3, and Period IV, Study 4 (Table 2).
† Baker's yeast was added to the basal diet during Periods II and IV, Study 1; Periods II, IV and VI, Study 3; and Period II, Study 4 (Table 2).

The yeast was consumed either fresh (mixed with water or fruit juice), boiled 2 minutes in water, or autolyzed 2 hours at room temperature with 2 ml. of ethyl acetate per cake of yeast. The autolysis was followed by boiling 1 hour to remove the acetate.

(Study 1) several 24 hour collections from each subject were composited to obtain a representative value for a single period.

Fecal collections were made except in Study 1. Fecal eliminations of 3 of the 6 subjects in Study 2 were collected. Charcoal and carmine were consumed on alternate

days to mark the feces. Each fecal elimination was collected directly in a 2% glacial acetic acid-alcohol mixture (Knott[8]). The samples were dried until brittle at 43° to 50° C. for 24 to 48 hours, ground and bottled. A 1 gm. aliquot was hydrolyzed with 20 ml. of 2N H_2SO_4 at 120° C. for 2 hours, neutralized with solid NaOH to about pH 3.5, filtered, and brought to a volume of 30 to 40 ml., and assayed for biotin content.

at 120° C. Six N H_2SO_4 for 4 hours at 120° C. liberated the maximum of biotin from beef liver.

Biotin was determined by a slight modification of the yeast-growth method of Snell, Eakin and Williams[17] with *Saccharomyces cerevisiæ* Strain 139. Test tubes 25 x 200 mm. in size were used instead of Erlenmeyer flasks. Three different amounts of the sample containing from 25 to 100 μμg. of biotin in a

TABLE 2.—URINARY AND FECAL BIOTIN DURING 4 STUDIES

Subjects, No.	Period No.	Period Days	Diets in various studies	Biotin intake (μg.)	Daily biotin elimination: Urine Range (μg.)	Urine Av. (μg.)	Feces Range (μg.)	Feces Av. (μg.)
			Study 1					
4	I	1–2	Basal*	21	22– 46	30		
	II	3–4	Basal + 3 boiled yeast cakes*	45	21– 29	26		
	III	2	Basal*	21	21– 31	27		
	IV	2–4	Basal + 3 fresh yeast cakes*	45	21– 30	26		
			Study 2					
6	I	3	Basal*	35	20– 36	28	57–106	82
	II	4	Basal + 4 boiled yeast cakes*	69	20– 39	30	17–114	65
	III	2	Basal*	35	21– 33	28	52– 73	61
	IV	4	Basal + 4 fresh yeast cakes*	69	16– 37	26	27–107	71
	V	2	Basal*	35	25– 37	33	39– 83	65
	VI	4	Basal + 4 autolyzed yeast cakes*	69	22– 49	35	20–109	75
	VII	3	Basal*	35	16– 39	27		
			Study 3					
2	I	1	Unrestricted	..	27– 35	31	105	
	II	1st	Basal with beef*	21	24– 37	31	57–202	132
	II	2nd	Basal with beef*	21	25– 40	32	65– 72	69
	II	3rd	Basal with beef*	21	25– 37	31	53– 72	63
	II	4th	Basal with beef*	21	33	33	20–123	72
	III	1st	Basal with beef liver	161	90– 95	93	48– 51	49
	III	2nd	Basal with beef liver	161	128–146	137	48– 75	61
	III	3rd	Basal with beef liver	161	114–183	148	65– 78	71
	III	4th	Basal with beef liver	161	141–165	153	36– 62	49
	IV	1	Unrestricted		84– 91	87	90	90
			Study 4					
3	I	3	Basal*	36	11– 34	23	41– 61	50
	II	4	Basal + 7½ boiled yeast cakes	93	20– 42	27	65–101	84
	III	3	Basal*	36	11– 29	22	66–118	91
	IV	4	Basal with beef liver	122	30– 83	60	72– 81	76
	V	4	Basal*	36	19– 59	33	55–100	72

* 1 mg. of thiamine hydrochloride added daily to basal diet.

The biotin content of the food was determined on aliquots of the foods consumed by the subjects. The weighed aliquots were homogenized in a Waring blender, hydrolyzed, neutralized and filtered in the same manner as the fecal samples.

The biotin contents of the beef liver and bakers' yeast were assayed separately from the rest of the foods. A maximum amount of biotin was liberated from the yeast by the methods tried with 4N H_2SO_4 for 4 hours

maximum of 2 ml. of solution were used. These levels of biotin are within the part of the standard curve obtained with pure biotin which forms a straight line. The addition of casein hydrolysate increases the range of biotin concentrations which can be measured by this method according to Hertz.[7] The curves for concentrations of pure biotin by the method of Snell *et al.*[17] and Hertz[7] coincide at the levels measured in the present studies.

The turbidity produced by the yeast growth in a sample tube after incubation at 30° C. for about 16 hours was compared with that of free acid biotin in an Evelyn photoelectric colorimeter using a 540 μ filter. If the three levels of the same sample did not agree within 10% of the lowest figure, the assays were repeated.

Results and Discussion. The urinary output is generally assumed to represent an excess of a vitamin not retained by the body and is believed to be an indirect indication of the amount used for maintenance, growth or storage. Thus, when the output of biotin exceeds the dietary intake there is either synthesis (Oppel[13]), removal from body stores or a combination of these two factors. Oppel[13] found relatively "normal" biotin excretion in fasting human subjects and those consuming egg-white for short periods. Therefore, he suggests that the level of urinary biotin is based on "biotin synthesis by colonic bacteria, and superimposed on this, sudden variations . . . due to changes in biotin content of the diet."

The urinary biotin of the 10 subjects during Studies 1 and 2 (Table 2) was not increased when the biotin intake was doubled (21 μg. increased to 45 μg. in Study 1, 35 μg. to 69 μg. in Study 2) by the inclusion daily of 3 or 4 cakes of fresh or boiled yeast. Urinary biotin during the basal periods accounted for an average of 110% of the biotin intake, while only an average of 45% of the intake appeared in the urine when fresh or boiled yeast was consumed. The absolute amounts of biotin excreted during the basal periods and the periods with fresh or boiled yeast were almost identical (average of 29 μg. for basal periods; 28 μg. for fresh and boiled yeast periods). These results are in contrast to the human utilization of thiamine and riboflavin in yeast in Study 1 (Parsons and Collord[14]). These workers found 2 to 3 times as much thiamine excreted when boiled yeast in contrast to fresh yeast was eaten. The excretion of riboflavin followed the same tendency.

When the yeast was autolyzed with ethyl acetate (Period VI, Study 2, Table 2), the urinary biotin rose only slightly for the 6 subjects, an average of 5 μg. daily over the basal periods which is equivalent to only 15% of the biotin in the ingested yeast. This slight rise in urinary biotin contrasted markedly with the sharp rise when beef liver was eaten (Study 4, Table 2).

Apparently at this level of biotin intake (69 μg.) variations in urinary excretion of biotin were nearly masked by the relatively large amounts of biotin synthesized by intestinal bacteria as indicated by the total biotin eliminated during each of the four studies (Table 2). Only at quite high levels of biotin intake such as during the periods of liver feeding of Studies 3 and 4 did the variations in urinary biotin stand out clearly from the interfering synthesis. Other factors in addition to changes influencing microbiological synthesis of biotin, which might account for the lack of consistent urinary response to ingestion of yeast biotin are: lack of utilization of biotin from yeast, perhaps due to lack of solubility; a retention of biotin by the body; or a combination of the above.

The water-soluble biotin of the fresh, boiled and autolyzed yeast amounted to 10, 10 and 21%, respectively, of the total biotin in the yeast ingested and on a weight basis equaled 3, 3 and 6 μg. per day (Study 2). If the proportion of biotin which is water-soluble is a measure of its availability to the animal, then one might expect the biotin of fresh and boiled yeast to be absorbed similarly and the ethyl acetate treated yeast to be more completely available. Some evidence of difficulty in digesting fresh yeast is indicated by the work of Montgomery *et al.*[10] who observed that over one-half of viable yeast cells passed through the stomach without being destroyed when fresh yeast was ingested. Viable yeast was found in feces of human subjects consuming fresh yeast but not for those consuming boiled yeast or an ordinary diet (Parsons, Williamson and Johnson[16]).

The fecal biotin for all four studies is

shown in Table 2. During the periods of yeast feeding (Study 2), the fecal biotin for the last 2 days averaged slightly higher (7 μg. higher daily) than during the corresponding days of the basal periods. Thus, the rise in fecal biotin accounted for only about 15% of the biotin intake from yeast.

An increase in fecal biotin could easily have been masked by changes in fecal synthesis, the yeast may have helped to make a medium less favorable for intestinal synthesis or the biotin contained in the yeast may have been utilized by the microörganisms in lieu of biotin synthesis by them. The possibility must be considered of a retention of biotin during the yeast periods, although there is no aparent reason for this inasmuch as the intake of biotin was rather liberal (Study 2).

It is possible that a longer period of adjustment to fresh yeast is necessary to reach an equilibrium in biotin excretion. There is some evidence to substantiate this need since the urinary biotin output during the basal period (V) following the ingestion of fresh yeast was noticeably higher than during the other two basal periods (III and VII, Study 2, Table 2). The first basal period is disregarded since this represents a transition from the unrestricted diet.

The purpose of Studies 3 and 4 was to determine whether or not urinary biotin could be elevated by the inclusion of moderate or large amounts of beef liver (77 and 185 gm.) and to compare the utilization of similar amounts of biotin from boiled bakers' yeast and beef liver (Study 4, Table 2). The biotin content of the diet was increased from 21 to 161 μg. daily (Study 3) and from 36 to 122 μg. (Study 4) by substituting beef liver for ground beef. The urinary biotin doubled or trebled on the first day of ingestion of liver and continued to rise for 3 or 4 days for both levels of liver feeding. A maximum of 183 μg. of urinary biotin was reached for 1 subject (Study 3). A longer period is probably necessary to reach a plateau of biotin excretion on such high levels of intake. This possibility was later substantiated (Gardner, *et al.*[3a].)

When the feeding of ground beef was resumed, the fall in urinary biotin was as rapid as was the rise during liver feeding. A comparison of the utilization of somewhat similar amounts of biotin from bakers' yeast and beef liver was made in Study 4 (Table 2). The inclusion of $7\frac{1}{2}$ cakes of boiled yeast daily increased the biotin intake from 36 to 93 μg. and 77 gm. of beef liver increased the intake from 36 to 122 μg. daily. Despite the large amount of boiled yeast, the urinary biotin was raised only 3 to 5 μg. daily for each of the 3 subjects (Table 2). These results corroborate those of Studies 1 and 2.

There was, however, a definite increase (average of 34 μg. daily) in fecal biotin during the ingestion of $7\frac{1}{2}$ cakes of yeast (Study 4). The high fecal biotin which continued through the 2-day basal period (III, Study 4) following the yeast feeding may also have been due to the yeast. In contrast, the fecal biotin was not significantly changed by the inclusion of liver (Study 3). During Study 4 the level of fecal biotin actually dropped from 91 to 76 μg. (daily average) during the liver period. As in Study 3 the increased total biotin excretion during liver feeding was due to increased urinary output of biotin, while the reverse was true during yeast feeding.

The importance of fecal biotin is difficult to ascertain in the first place because it may be derived from several sources as follows: (1) unabsorbed food, (2) biotin absorbed from the gastro-intestinal tract and reëxcreted, (3) biotin removed from body stores, and (4) biotin originating from microörganisms. With present methods it is not possible to assign the source of biotin which is eliminated or excreted. Secondly, the question of absorption from the large intestinæ of biotin or other substances synthesized by microörganisms needs reëxamination since most of the intestinal flora occur below the level at which most of the absorption of nutrients other than water is believed to take place.

Najjar and coworkers[11,12] have recently reported absorption of thiamine and riboflavin by man from the large intestine after large amounts of these vitamins were administered by a "retention" enema. On the other hand, Alexander and Landwehr[1] found no evidence of absorption of physiologic amounts of thiamine given in a similar manner. Mitchell and Isbell,[9] however, found that in rats the biotin and pyridoxin synthesized by intestinal bacteria apparently moved freely from the bacterial cells into the surrounding medium and were, therefore, available for absorption.

The total output of biotin during Studies 2, 3 and 4 is interesting. The range of total output varied from 54 to 261 μg. per diem which accounted for from 86 to 1073% of the dietary biotin. Each of these values is for 1 day for a single individual. The greatest excess of biotin output over intake occurred during the periods of lowest intake, *i. e.*, during the basal periods. The average output during all of the basal periods of Studies 2, 3 and 4 was 100 μg. daily or about 300% of the biotin intake.

During the periods of yeast feeding the total biotin output averaged 103 μg. daily or 137% of the intake, during the liver feeding 163μg. or 115%. Only on single days did the biotin output fall below the intake, *e. g.*, the first day of liver feeding (Study 3). Since the biotin output nearly always exceeded the intake, synthesis of biotin probably by microörganisms is indicated. It would appear that less biotin was synthesized during the ingestion of bakers' yeast and beef liver as compared with the basal periods.

Summary. Four studies of the biotin metabolism of 15 college women who consumed uniform diets and these same diets supplemented with bakers' yeast or beef liver are presented. These diets contained from 21 to 161 μg. of biotin per diem.

Doubling the biotin intake by the addition of 3 or 4 cakes of fresh or boiled yeast per diem failed to cause a consistent rise in urinary biotin and only a minor rise in fecal biotin was observed. Four cakes daily of yeast autolyzed with ethyl acetate increased the urinary output about 18%, which is nearly equivalent to the water-soluble biotin from the treated yeast.

The daily addition of 7½ cakes of boiled yeast increased the urinary biotin somewhat (14 to 33%) while a somewhat larger amount of biotin from beef liver doubled or trebled the urinary output on the first day of liver feeding. The rise continued for 3 to 4 days.

The range of biotin output in urine and feces per diem was as follows: urine 11 to 183 μg., feces 17 to 208 μg., total 54 to 261 μg.

The total output amounted to less than 1 to 11 times the intake depending to a large extent on the diet. The greatest excess of output over intake occurred on low biotin intake and the least excess occurred on a high biotin intake during liver feeding.

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CHLOROMA—A CLINICO-PATHOLOGIC STUDY OF TWO CASES

By E. G. Goodman, M.D.
INSTRUCTOR IN MEDICINE
AND
Lalla Iverson, M.D.
ASSISTANT IN PATHOLOGY
DURHAM, NORTH CAROLINA

(From the Duke University School of Medicine)

Chloroma is a rare disease. The 2 instances reported in this paper are the only ones so diagnosed at Duke Hospital among 226,796 patients. In both instances tumors were the presenting signs, and the clinical course was rapidly downhill.

No attempt was made to review the literature. An excellent bibliography and résumé of the subject may be obtained from Forkner's book on "Leukemia and Allied Disorders."

Case Reports. Case 1. (Unit B-23978). *Clinical History.* A 7 year old colored boy was admitted to the Eye Service on Feb. 29, 1944, with a marked exophthalmos on the left. (Fig. 1.) A letter from the referring physician stated that the patient had had a throat and ear infection 2 mos. previously, and at that time developed a facial paralysis with edema of both eyes. One week before admission there was a recurrence of orbital edema, bilaterally, but more marked on the left. The patient was sent with a tentative diagnosis of retro-orbital tumor or cavernous sinus thrombosis.

Physical Examination. Temperature, 38.8°; pulse, 120; respirations, 22. The patient was a poorly nourished Negro boy, who was acutely ill and complaining of pain in the abdomen and left eye. There was a marked bony swelling over the left zygoma which was non-tender. The left eye almost protruded from the orbit, with marked chemosis and excoriations of the conjunctiva and edema of the orbit. (Fig. 1.) Some exophthalmos was present on the right, but no chemosis. There was a bilateral diminution of hearing. The abdomen was moderately distended and tympanitic. The liver border was barely felt. Remainder of physical examination was non-contributory.

Accessory Clinical Findings. Hemoglobin, 7.3 gm. (47%); erythrocyte count, 2,330,000; leukocyte count, 232,000, with the following differential formula: myeloblasts, 85%; undifferentiated myelocytes, 10%; neutrophilic myelocytes, 4%; and eosinophilic myelocytes, 1%. (Fig. 2.) Examination of the smear showed moderate anisocytosis and poikilocytosis. No nucleated red cells were seen. Platelets were 100,000 per c.mm. and reticulocytes estimated at 1%. Sternal puncture showed the leukocytes to number 480,000 per c.mm. There was a scarcity of nucleated red cells. Reticulocytes were estimated at 2%. There was a marked hyperplasia of the embryonic cells, similar to those seen in the peripheral blood. These cells were definitely myeloid. On dark-field examination the characteristic refractile granulation was present in the majority. Goodpasture stain gave a positive peroxidase reaction. In some, the nucleus was distorted, probably indicating mitosis. Differential on bone marrow: myeloblasts, 82%; undifferentiated myelocytes, 10%; neutrophilic myelocytes, 7%; eosinophilic myelocytes, 1%. An average of 1 erythroblast was seen for every 100 white blood cells. Blood Kahn, Kline, and Mazzini were negative. Roentgen rays of the sinuses showed a large soft tissue shadow overlying the left orbit. The right antrum and ethmoids on both sides appeared to be cloudy. Mastoid cells showed a somewhat hazy outline along the septa. A Roentgen ray of the chest showed a haze over the entire right chest, due to pleural reaction, and a fuzzy increase in lung markings in the right base and left upper lobe. No definite glandular enlargement was seen. Urine examination revealed a specific gravity of 1.104; reaction, acid; sugar, none; albumin, 3+. Microscopic examination of the sediment showed 3 to 4 white blood cells per high-power field and an occasional granular cast. Acetone reaction was 2+, and the test for diacetic acid was positive.

Course in Hospital. The patient was put at bed rest and sedated with codeine and

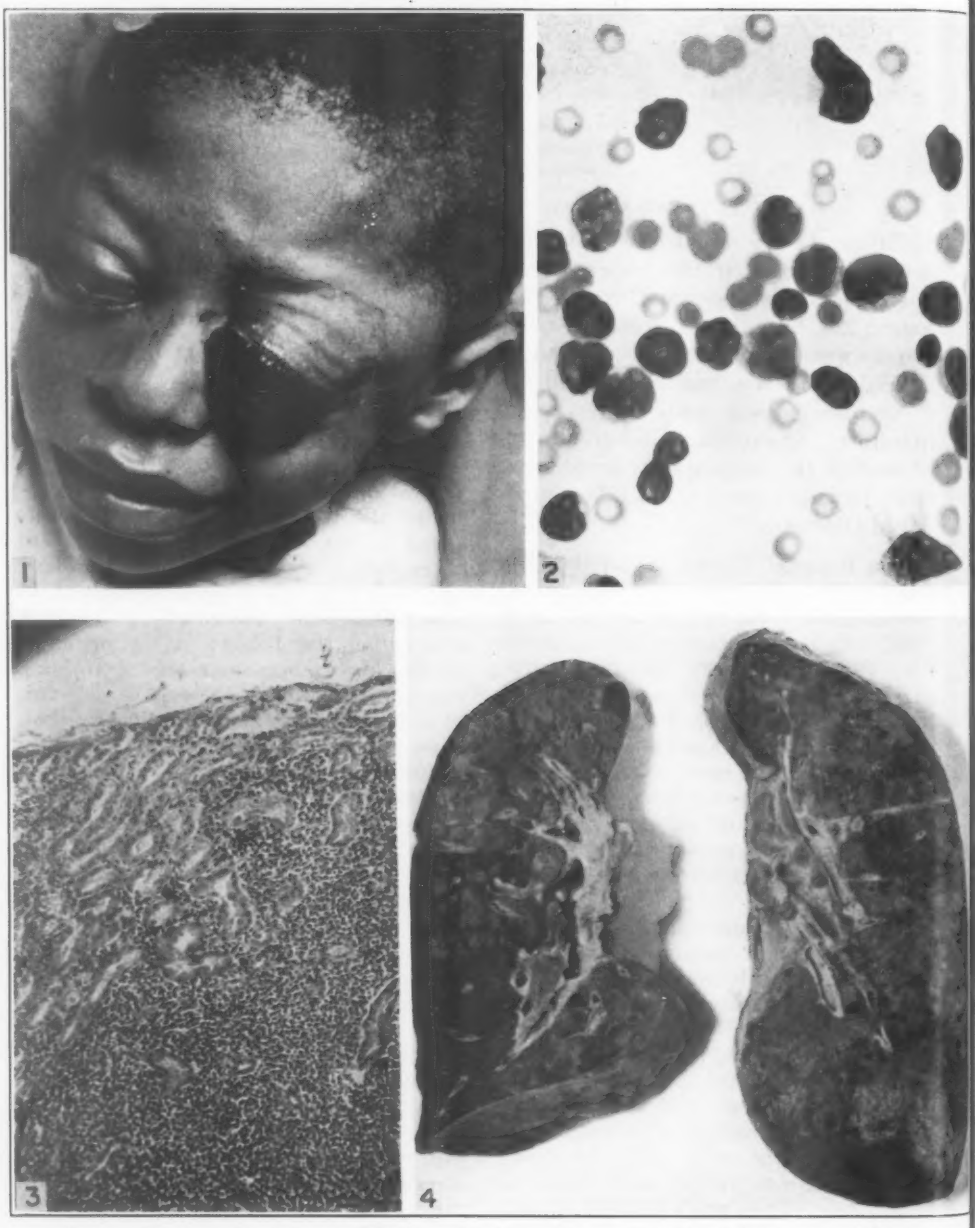


FIG. 1.—Case 1. At time of admission, showing extreme proptosis of left eye and beginning exophthalmos on right.

FIG. 2.—Case 1. Smear of peripheral blood, showing predominance of myeloblasts.

FIG. 3.—Case 1. Microscopic section of kidney showing compression and infiltration of kidney parenchyma by chloroma nodule.

FIG. 4.—Case 1. Lungs showing enlarged hilar nodes and massive consolidation.

aspirin whenever necessary for relief of pain. The left eye was protected by saline compresses. Four 250-cc. transfusions of whole blood were given and also several injections of intravenous dextrose. His temperature ranged between 38° and 40° C. for the first 4 days in the hospital. He was then started on 10 cc. of methylene blue (10 mg. per cc.) intravenously each day for 4 days. The temperature dropped below 38° C. while on this medication, but his pulse rate remained around 120. Because of the hopeless outlook and scarcity of veins, methylene blue was discontinued, following which his temperature again rose to the former level between 38° and 40° C. A clinical analysis of the urine revealed large amounts of porphyrin, but this was after the patient had received 2 blood transfusions. The patient became progressively worse and expired on the 15th hospital day.

Autopsy Findings. (No. 4022.) Acute myeloblastic leukemia; porphyrinuria; chloroma of right auricular appendage, kidneys, bladder, bile ducts, skull, scalp; (history of blindness), chloroma of right and left orbits with extreme proptosis, chemosis, keratitis, iritis; hepatomegaly, splenomegaly, general glandular enlargement; diffuse myeloid alteration of bone marrow, lymph nodes, liver, spleen, pleura, lungs, pericardium, diaphragm, choroid and sclera; petechial hemorrhage in epicardium, pleura, renal pelves, testis and retinæ; bilateral confluent lobular pneumonia, fibrinopurulent pleurisy, serosanguineous pleural effusion.

Gross Examination. Autopsy was performed 6 hours after death. The enlargement of the cervical, axillary and inguinal nodes was accentuated by the juvenile thin, bony body. Twelve small, firm, pea-sized, movable nodules were palpated in the scalp. The eyelids were stretched to 3 times normal size because of the extreme proptosis. Bloody, frothy fluid poured from the nose.

The centers of the enlarged mediastinal lymph nodes like those of the rest of the body were gray-green, exhibiting an infiltrating type of reaction, rather than the homogeneous alteration characteristic of lymphoid leukemias. No remnant of thymus could be identified in the small green mass of matted nodes attached to the upper anterior pericardium.

The right and left pleural cavities each contained 400 cc. of serosanguineous fluid. Shaggy fibrinopurulent adhesions covered the pleural surfaces of the lungs, which were completely solidified by hemorrhage, edema and confluent areas of pneumonic consolidation. (Fig. 4.)

Numerous petechiæ dotted the epicardium. A glistening lime-green nodule 0.7 cm. in diameter was found on the right auricular appendage, and a similar flattened mass was seen beneath the endocardium of the left ventricle.

The liver was twice its normal size. The endothelial lining of the larger vessels was a distinct light green. Two soft, rather friable, unencapsulated, olive-green masses, 3 x 2 x 0.5 cm., were located along the course of the common bile duct, surrounding but not obstructing it. The spleen was moderately enlarged, and its firm red pulp bulged from the tight capsule. The adrenals were normal.

Both kidneys were greatly enlarged. The cortex of each exhibited 4 or 5 small raised nodules with hemorrhagic borders and green centers. Several similar masses noted in the bladder wall were also characterized by the unique yellow-green color seen in varying concentrations in the urine, endothelium, connective tissue, and periosteum. (Fig. 6.)

Additional green nodules were seen in the scalp, calvarium, and dura. No lesions of the brain or cranial nerves were demonstrated.

Attached to the periosteum of the posterior portion of each orbit was a soft flattened dirty green mass which extended inferiorly to the sheath of the optic nerve and laterally to the lacrimal glands. Dense infiltration of the orbital fat, choroid, and sclera were noted, in addition to the small retinal hemorrhages. There was edema, inflammation, and necrosis of the conjunctiva, cornea, and iris. (Fig. 5.)

At the time of autopsy hydrogen peroxide restored the green color to the faded fresh tissue. This was not observed later on the formalin-fixed tumors. Four months after autopsy, portions of the formalin-fixed tissue were treated with glacial acetic acid and ether, and the extract examined spectroscopically for proptoporphyrin, with negative results.

Bacteriology. Beta hemolytic streptococci were grown from the spleen and both lungs.

Microscopic Examination. The sections were stained with hematoxylin and eosin, Wright's stain, and Giemsa. Each oil im-

mersion field of the chloroma masses contained several eosinophils, 1 or 2 segmented neutrophils, and a few juvenile and stab forms. With the help of peroxidase and oxidase stains, most of the cells were identified as myelocytes and myeloblasts. Neutral red and brilliant cresyl blue preparations were not contributory. Scharlach Red sections on formalin-fixed tissue showed tiny round droplets of fat in the periphery of cells resembling myelocytes and metamyelocytes. The polarized light microscope failed to show any doubly refractile crystals in the chloroma mass from the left kidney.

Remnants of lymphoid follicles were noted in the "chloromas" adjacent to the bile ducts. Special stains revealed a fine reticulum of that density seen ordinarily in lymph nodes. Small blood-vessels with a fine fibrous support were moderately prominent. The tumors were not encapsulated, and the gross appearance of circumscribed nodules was found to be due to an abrupt change in the concentration of cells in the tissue. This was especially striking in the kidneys where the distribution of cells strongly resembled metastatic lymphosarcoma. (Fig. 3.)

The liver, spleen and lymph nodes ex-

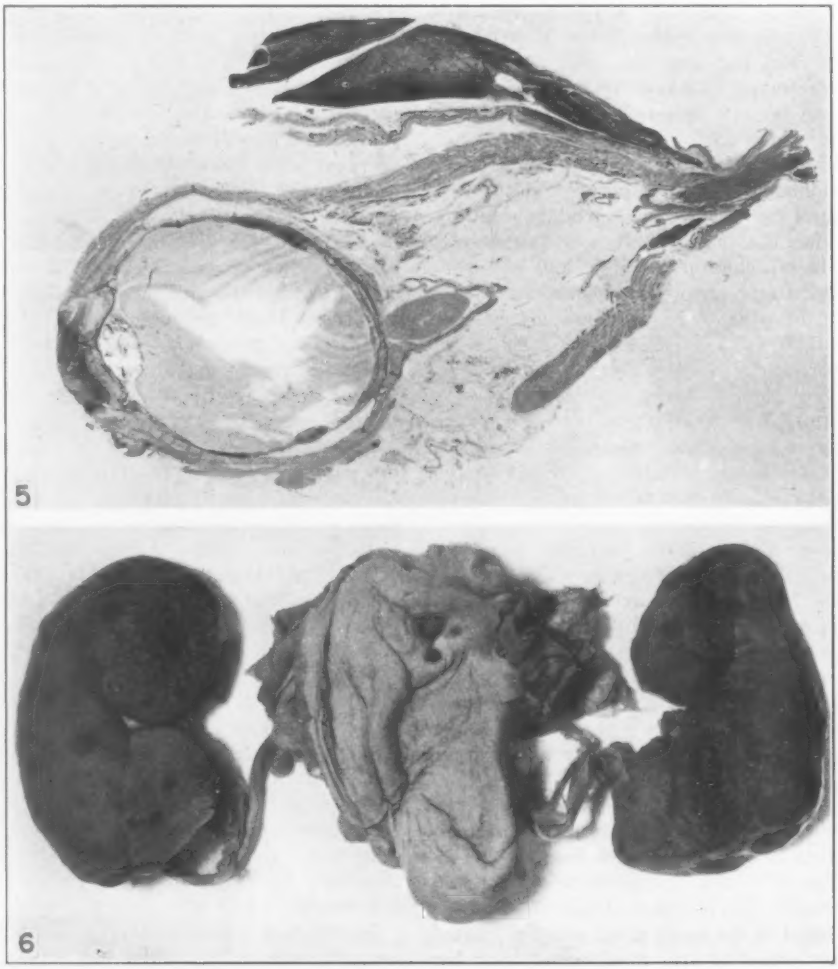


FIG. 5.—Case 1. Low-power view of orbital tissue. Note large chloroma in superior and posterior orbit and sprinkling of cells about optic nerve, muscles, and retina.

FIG. 6.—Case 1. Urinary tract showing many nodules in both kidneys and in bladder. Note hemorrhagic borders of chloroma.

hibited the diffuse infiltration typical of myeloid leukemias, whereas the bone marrow was filled with proliferating cells. Many gram-positive cocci were stained in the consolidated portions of the lungs. These were accompanied by a massive infiltration of early myeloid cells.

Case 2. (Unit B–26796). *Clinical History.* A 33 year old married male was admitted on April 14, 1944, because of a suspected brain tumor. He dated the onset of his illness 6 weeks previously, when he struck his head on a weight, after which a small nodule appeared on the occipital area of his head. The nodule grew rapidly and was excised. On study of sections of this tissue, the pathologist was unable to make a definite diagnosis. Three weeks following the initial episode, he developed severe occipital headaches radiating down the left side of his neck. He was admitted to another hospital, and while there developed diplopia and left-sided weakness. During the hospitalization, 2 lumbar punctures were done, and the spinal fluid found to be under increased pressure. He was referred with a tentative diagnosis of brain tumor.

Physical Examination. Temperature, 37.8°; pulse, 99; respirations, 18; blood pressure, 130/75. The patient was a well-developed and well-nourished young man who was acutely ill and quite uncomfortable. All of the superficial lymph nodes were palpable, firm, shotty, movable, and non-tender. The face was asymmetrical due to a left facial palsy, and there was some proptosis of the left eye. (Fig. 7.)

Numerous petechiæ were scattered over the abdomen and back. There was tenderness on palpation over the left parieto-occipital area. The right pupil was much larger than the left and reacted well to light and on accommodation. The left pupil was miotic, failed to react to light, and appeared to be irregular. Extraocular movements were poorly performed due to failure of the left lid to move well and to a sixth nerve weakness. There was a bilateral diminution of hearing. There was slight pain on flexion of the neck. The chest was symmetrical and expansion was equal; however, there was a small tender nodule felt over the xyphoid process. Respirations were mainly abdominal. The lung fields were clear. No cardiac abnormalities were noted. The abdomen was flat without tenderness or spasm. The liver border was palpable a few finger-breadths below the costal margin. The tip of the spleen was barely felt. A detailed neurologic examination revealed the following pertinent findings: (1) Bilateral papilledema with multiple exudates, hemorrhages, and scars located around the nerve heads; the retinal veins were engorged and tortuous; (2) the pupils were unequal, the right being much larger than the left; the extraocular movements were poorly performed due to sixth nerve weakness on the left; (3) there was hypalgesia over the left face, and the corneal reflex was absent on the left; (4) there was a left lower facial weakness; (5) hearing was bilaterally diminished and audiograms revealed a nerve deafness bilaterally; (6) the motor and sensory systems were intact elsewhere; reflexes were equal and active, and Babinski was negative.

Accessory Clinical Findings. Hemoglobin, 12.1 gm. (78%); erythrocyte count, 3,940,000; leukocyte count, 29,000. The differential formula revealed the following: segmented neutrophils, 5%; myeloblasts, 77%; undifferentiated myelocytes, 9%; neutrophilic myelocytes, 1%; micromyeloblasts, 1%; small lymphocytes, 5%; large lymphocytes, 1%; plasma cells, 1%. (Fig. 8.) The erythrocytes showed only slight variation in size and shape. No nucleated red cells were seen in the peripheral blood. Reticulocytes were estimated at 2%. Platelets were reduced to 100,000 per c.mm. Bone marrow studies showed a leukocyte count of 80,500 per c.mm. There were numerous myeloblasts and an occasional nucleated red cell. Differential formula: segmented neutrophils, 2%; myeloblasts, 55%; micromyeloblasts, 29%; differentiated myelocytes, 8%; eosinophilic myelocytes, 1%; small lymphocytes, 4%; large lymphocytes, 1%. An average of 1 erythroblast per 100 white blood cells could be counted. It was the impression of the hematologic consultant that this was an instance of myeloblastic leukemia and that the central nervous system findings could be explained on the basis of chloroma.

Blood Kahn, Kline, and Mazzini were negative. Blood NPN was 29 mg. %; serum calcium, 9.1 mg. %; phosphorus, 4.3 mg. %; serum protein, 6.6 mg. %. Roentgen ray of the chest showed a diffuse increase in the lung markings with an area of increased density in the right upper lung field. Roent-

gen rays of the abdomen, spine, and pelvis showed nothing abnormal; no abnormal calcifications were seen in Roentgen ray of the skull. An electroencephalogram showed slight irregularities over the right occipital area, but otherwise the record was within normal limits. Visual fields were normal. Routine urine examination was negative. Urinary porphyrins were not increased. A lumbar puncture revealed tremendously increased pressure, measured at 430 mm. of spinal fluid. There were 33 leukocytes and 10 red blood cells per c.mm. of spinal fluid. Pandy reaction was slightly positive, and spinal fluid proteins measured 43 mg. %. The Wassermann and colloidal mastic test on the spinal fluid were negative.

Course in the Hospital. After 8 days of supportive therapy and multiple small transfusions, the patient failed rapidly. His abdomen became distended, and he was unable to swallow. There was marked urinary retention, which continued until death. New hemorrhages appeared in the left eye, and the papilledema became worse. Exophthalmos on the left became more prominent. Cheyne-Stokes respiration developed several days before death. On the day before death,

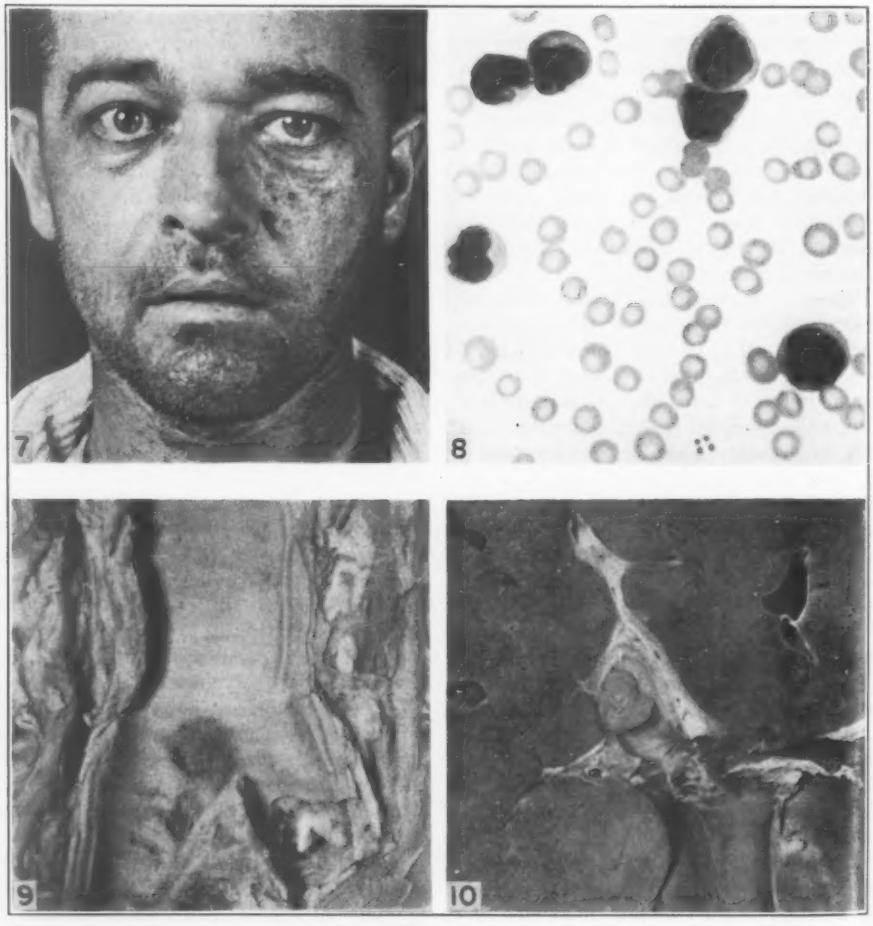


FIG. 7.—Case 2. Photograph on admission showing beginning exophthalmos of left eye.
FIG. 8.—Case 2. Smear of peripheral blood showing myeloblasts.
FIG. 9.—Case 2. Small nodule at bifurcation of trachea.
FIG. 10.—Case 2. Section of liver showing soft, well-circumscribed nodule hanging from wall of portal vein.

the left eyeball was practically protruding from the orbit, and the right eye exhibited papilledema, hemorrhage, and exudate, and bleeding continued into the skin, mucous membranes, and eyegrounds. By this time the hemoglobin had dropped to 7.8 gm. (50%), in spite of frequent transfusions; the red cell count was 2,280,000. The white count of 25,480 and the differential formula were essentially as on admission. The patient died on the 16th hospital day.

Autopsy Findings. (No. 4071.) Acute myeloblastic leukemia; chloroma of dura, trachea, mediastinum, liver, kidneys; periosteal and perichondrial chloroma of ribs, sternum, thoracic and sacral vertebræ; chloroma of left orbit, exophthalmos, chemosis, keratitis, and iritis; hepatomegaly, splenomegaly, moderate general glandular enlargement; diffuse myeloid alteration of pleura, meninges, spleen, lymph nodes, liver, and bone marrow; petechial hemorrhages of skin, gums, stomach, intestines, bladder, prostate and testis, subdural hemorrhage, cystitis, cardiac dilatation; congestion of lungs, liver, and spleen.

Gross Examination. Autopsy was performed 11 hrs. after death. The body was covered with bruises and numerous petechiæ. There was a faint yellow tinge to the inelastic skin and to the sclera of the right eye, which protruded slightly. The left eye exhibited marked chemosis because of the prominent exophthalmos.

The external and internal surfaces of the ribs, manubrium, and sternum were almost completely covered by varying concentrations of soft, grayish green tissue which also transformed the vertebral column into a smooth, shiny green ridge. (Fig. 11.) In the thoracic cavity a solid rope of green tissue, 8 x 2 x 2 cm., separated the esophagus and aorta; and in the pelvis the rectum was matted to the sacral vertebræ by a similar mass.

Although there was slight general lymphoid hyperplasia, only the mediastinal and cervical lymph nodes were moderately enlarged, containing yellow-gray centers suggestive of leukemoid infiltration. A remnant of thymus was embedded in a mealy grayish green mass, 3 x 2 cm., matting together the anterior pericardium and adjacent mediastinal fascia. A soft green nodule, 1.7 cm. in diameter, projected into the lumen of the trachea. (Fig. 9.) The posterior pleural surfaces of the edematous and congested lungs were infiltrated locally by extensions from the adjacent costal masses. (Fig. 12.) At the porta of the enlarged liver was a chloromatous nodule projecting through the wall of a vein into its lumen, and smaller ocalized masses marked several of the portal areas. (Fig. 10.)

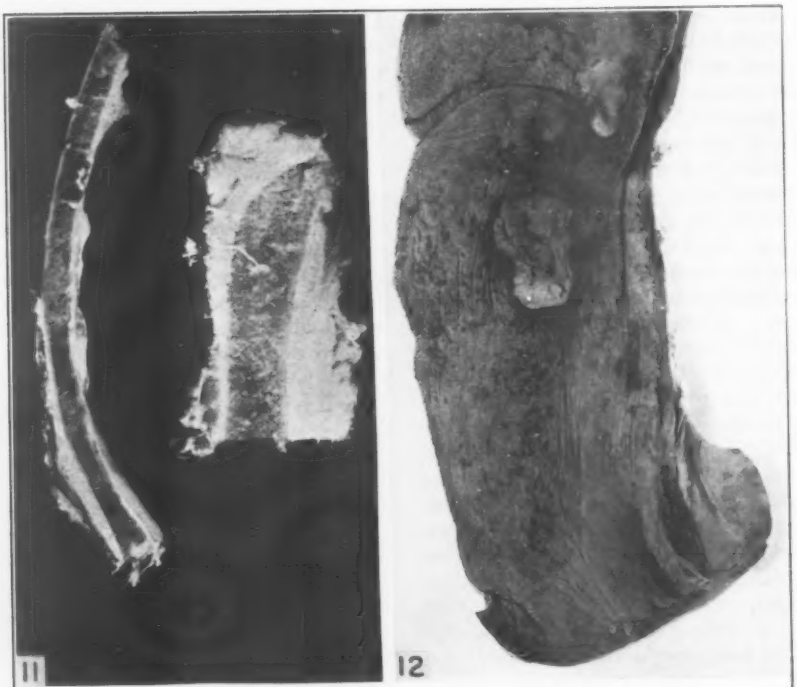
The adrenals were normal. Each kidney weighed 200 gm. and showed minute hemorrhagic cortical nodules, pelvic hemorrhages and extreme thickening of the upper calyces by infiltration of grayish green tissue, the faded color of which was restored slightly with hydrogen peroxide. This phenomenon was not duplicated with formalin-fixed tissue 2 mos. later.

Examination of the skull revealed no nodules at any of the foramina. However, the meninges of the medulla, pons, base of brain, and sella turcica were slightly thickened. Several circumscribed pea-sized masses were seen on both surfaces of the dura. Beneath the dura on the left these nodules were covered by a thin coat of fresh and clotted blood extending over the entire left parietal lobe.

In the posterior portion of the left orbit was a flat disk of dirty green tissue, 4 x 2 x 1 cm. Spectroscopic examination of the formalin-fixed tissue 2 mos. after autopsy was negative.

Microscopic Examination. Sections of the rib, sternum, vertebra and femur showed the marrow to be entirely replaced by cells of the myeloid series, 80% of which were similar to those in the green tumors identified as myeloblasts by peroxidase stains. The blood-vessels showed qualitative, rather than quantitative, change in the character of the circulating leukocytes. Likewise, the sinusoids of the liver were not greatly infiltrated, except at the sites of the nodular accumulations of myeloid cells seen grossly. The pleura, lungs, renal cortices, lymph nodes and spleen showed slight but definite myeloid alteration.

The solid tumors were held together by a light fibrous stroma. No lymphoid tissue was demonstrated in the masses adjacent to the aorta, rectum, and periosteum. Special stains of these showed a light, fine reticulum. Scharlach R preparations of the formalin-fixed tissue revealed small fat droplets in the cytoplasm of some of the earlier myeloid



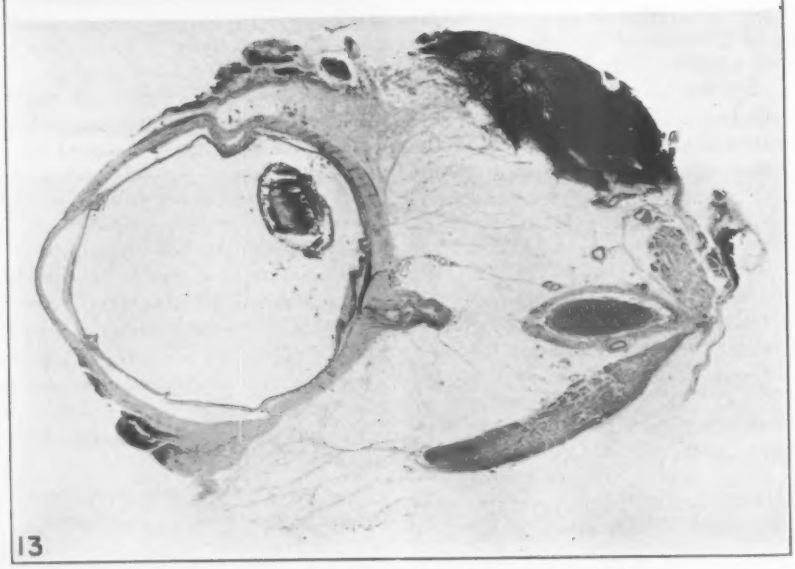


FIG. 11.—Case 2. Rib and sternum showing relation of tumor to periosteum.
FIG. 12.—Case 2. Posterior surface of left lung and masses of chloroma tissue which had extended from the adjacent rib.
FIG. 13.—Case 2. Lantern slide of eye and relation of chloroma to orbital tissue.

cells. Polarized light studies revealed no doubly refractile crystals.

The meninges over the medulla and pons were thick with myeloid cells, and occasional perivascular foci within the pons and cranial nerves were seen. Sections of the left eye showed the tips of the lacrimal glands to be embedded in the large chloroma, which also involved the periosteum of the orbit, Tenon's capsule, and the sheath of the optic nerve. The cells separated the muscle fibers and loosely infiltrated the orbital fat, posterior retina, sclera, and choroid. The iris and cornea, altered by inflammation, edema, and necrosis, exhibited no leukemic infiltration. (Fig. 13.)

Discussion. The 2 patients described showed the following clinical characteristics:

1. The presenting symptoms and signs of a rapidly growing tumor in both cases producing extreme exophthalmos.

2. The hematologic picture of an acute myelogenous (myeloblastic) leukemia.

3. A rapidly downhill course.

In Case 2 the neurologic picture was one of an infiltrating lesion in the pons, but autopsy showed only meningeal infiltration in addition to the other findings described above. In both instances the correct diagnosis was made before death.

The exact nature of the pigment which causes these peculiar "green tumors" is unknown. It is thought to be chemically related to the porphyrins. Because of this, urinary porphyrin determinations were made. The first case showed large amounts of porphyrin in the urine, the significance of which is questionable because of the transfusions given previously. In the second case porphyrin determinations were made before transfusing the patient, and there was no appreciable increase in urinary porphyrins.

At autopsy further attempts were made to study the pigment. Hydrogen peroxide characteristically restored the pigment in the fresh tissue. Polarized light studies and spectroscopic analysis were performed on formalin-fixed tissue with no contributory results. Scharlach Red stains, however, revealed a few minute fatty droplets in the cytoplasm of cells resembling earlier myeloid cells.

At autopsy the pigment was not only confined to the tumor masses, but was distributed homogeneously throughout connective tissue, mucosal surfaces, and endothelial lining. This interesting and unusual distribution is reminiscent of that of the bile pigments in cases of jaundice, and confirms previous observations that the pigment is located in the plasma of the circulating blood. We believe that it represents there an intermediary product, protoporphyrin, in the breakdown of hemoglobin to bilirubin. This is further substantiated by the fact that, although the duration of both of our cases was equal, the concentration of green pigment was greater in Case 1, in which the hemoglobin was 7.3 gm., compared to 12.1 gm. in Case 2.

The observations of these cases are in accord with those reported in the literature. The great variation in gross morphology and distribution should be emphasized.

Cases have been reported earlier in which chloromatous masses have been associated with lymphatic leukemia, monocytic leukemia, and lymphosarcoma. The hematologic methods in these cases, however, are not reliable and do not compare with techniques used today for identification of myeloblasts. It is our impression, therefore, that chloroma represents an atypical form of myeloblastic leukemia, and in distribution of cells is related to myelogenous leukemia as lymphosarcoma is related to lymphatic leukemia.

Summary. 1. The clinical and pathologic findings of 2 cases of chloroma have been presented, with results of special studies as to the nature of the green pigment characteristic of these tumors.

2. Chloroma represents a rare form of myeloblastic leukemia in which the cells show an unusual tendency toward tumor formation.

3. The pathologic findings herewith photographed and described indicate that

chloromas may be present as small, well-circumscribed nodules or as large, solid masses with particular predilection for meninges, periosteum, mucous membranes, endothelium, and mesothelium.

4. Although the exact chemical nature of the green pigment has not been demonstrated by our spectroscopic and polariscopic studies, the distribution in the above cases suggests an intermediary product in the breakdown of hemoglobin to bilirubin.

5. "Chloroma" should be suspected clinically when tumors occur coincidentally with a myeloblastic leukemia.

THE NATURAL COURSE OF CHRONIC SOUTHWEST PACIFIC MALARIA

By Major William L. Noe, Jr., M.C., A.U.S.
Captain Clyde C. Greene, Jr., M.C., A.U.S.
and
Lt. Col. Garnett Cheney, M.C., A.U.S.
APO 827, New Orleans, Louisiana.

Definite knowledge concerning the natural course of chronic Southwest Pacific vivax malaria is lacking. Such a knowledge is of unusual importance at present, not only because of the large number of cases that are being observed, and because their management is unsatisfactory, but also because the effects of various forms of treatment cannot be evaluated until they are compared with the natural course of the disease when it is untreated. The generally accepted concept of the clinical course of vivax malaria is that it is a febrile disease manifested by periodic bouts of activity which are characterized by chills, fever and sweating. The periodicity is classically shown by the fever appearing on alternate days with free intervals in between, producing the well-known temperature pattern of tertian malaria. It is widely recognized that the original attack may be of short or long duration, and that there is a marked tendency for the infection to become chronic and manifest itself by relapses which resemble the original attack. However, there is no accurate information at present on whether or not the natural course of malaria in the Southwest Pacific area corresponds to the generally accepted concept of the disease which has been based on observations of malaria made in other parts of the world.

Known Effect of Anti-malaria Therapy. Although the suppressive therapy of malaria by atabrine has been proven quite satisfactory since sufficient atabrine has been administered to produce blood levels which are incompatible with parasitemia, it is recognized that suppression of clinical malaria by atabrine is of temporary value and only effective as long as the atabrine treatment is continued. It is also known that treatment of each acute attack of malaria by a week's course of atabrine therapy is only satisfactory in aborting the attack, and does not prevent relapses from recurring. Publications are still appearing discussing the curative treatment of malaria,[3] but there is no known curative treatment. Quinine is no more effective than atabrine, but it has been used very little recently because of the shortage of supply. Other forms of treatment have not proven equal to atabrine and quinine in effectiveness.

The question of the development of immunity to malaria is an important one. Immunity does develop and is parasite-strain specific, but its acquisition takes a long period of time which varies greatly in individual cases. It is known that prolonged clinical activity occurring in a patient with therapeutically induced malaria may cause the rapid development of immunity to native American strains, and the patient may become cured in the full sense of the word providing no drug treatment is given.[1] It has been suggested that Southwest Pacific malaria may also develop immunity resulting in cure if treatment is withheld.

The Natural Course of Relapsing Malaria. In a study recently carried out at Hammond General Hospital, it was planned to observe the natural course of relapsing Southwest Pacific malaria without treatment in order to ascertain whether or not immunity might develop with sufficient rapidity to warrant the clinical use of so-called "non-specific therapy" (no treatment) in the management of the malaria problem in soldiers returning from the Pacific area. While carrying

out this program, specific treatment was withheld as long as the patient's clinical condition was satisfactory; but in every instance the patient had received suppressive treatment overseas or treatment of the original attack overseas so that his clinical malaria was only untreated in the later stages, and its complete natural course may have been altered by therapy carried out before coming under our observation. However, we were able to study 72 patients who volunteered to take part in the program, and in 23 of them no specific treatment of any sort was ever carried out at Hammond General Hospital. In 19 others specific treatment was utilized for administrative reasons only at some one time during the observations made, and 17 cases had to have drug therapy for all clinical activity because of the severity of their infection. Two patients had parasitemia only.

Although we have made no initial observations from which to illustrate the early course of the disease, a number of reports indicate that at onset fever occurs irregularly and does not follow the common tertian pattern. The duration of fever is also variable and there is nothing about the temperature chart to suggest vivax malaria as it is usually described in standard texts.[2] We have, however, been able to identify the manifestations of the onset of this disease in other patients who were under suppressive atabrine therapy in the Southwest Pacific area, and, subsequently developed their first clinical attacks of malaria in the United States. This initial period of onset of the disease has been designated as Phase 1, and probably the majority of patients in this phase have no recurrences following one or two attacks. However, once the disease becomes chronically relapsing, it assumes a somewhat different course.

Present Study. The patients under observation started on the program having previously had from 1 to 16 relapses. The average number of previous attacks per patient was 6.64 for 69 patients. As a rule, each acute relapse had been treated previously. We have designated this chronic relapsing stage, in which frequent recurrences have become well established, as Phase 2 or the intermediate phase of the disease (Chart 1). When drug therapy is withheld, the natural course of Phase 2 is typified by relapses, each of which may include recurrent "bouts" of chills and fever. These "bouts" of clinical activity tend to assume the single tertian pattern, but may assume a double tertian pattern. Each relapse may last from 1 day to more than 3 months. The average duration of 113 untreated attacks was 5.47 days. Between these "bouts" of fever (fever is taken to be a temperature of 100° F. by mouth or over) there is usually clinical activity in that the patients do not feel well and there may be headache, some generalized aching and slight rises in temperature. The blood studies usually reveal the presence of parasites during the active periods of this phase. Clinical activity may subside after a single "bout" of fever, or may recur for months.

Following this second phase which is punctuated by irregularly occurring "bouts" of clinical activity with parasitemia, a third phase of the disease occurs which may be terminal. During this final phase there are few or no clinical symptoms, and the temperature does not rise above 100°, but parasitemia is constantly or irregularly present. Phase 3 lasted from 10 to 80 days in 30 cases which were completely followed, and apparently represents the development of immunity and perhaps cure (Chart 2). However, even after a patient has passed through all three phases of the disease, an occasional late relapse might occur. No such relapse was noted in our series during the period of follow-up observation which was continued for at least 3 months in each case of the entire series.

Results of the Special Program Study. The patients on this non-specific malaria therapy program were under observation for from 2 to 10 months. The natural course of the disease during the second

and third phases seems to have been sufficiently well studied to draw the conclusion that Phase 2 ordinarily takes many months, and that Phase 3 may last many weeks. This makes the therapeutic procedure of inducing immunity by withholding drug therapy an impractical procedure in military medicine. However, the observations carried out make possible a clearer conception of the disease and certainly afford a better basis for judging the effects of treatment than has heretofore been possible. This is well illustrated by the fact that the cyclic recurrences which have been considered so characteristic of Southwest Pacific malaria very rarely occurred when treatment was withheld. In 1943 in calculating the incidence of relapses in a series of 169 atabrine treated cases, we found that there were 424 attacks in the group, when relapses were analyzed in patients having up to 11 attacks. In the majority of these patients, the period between attacks was so constant that the time of the next attack could be predicted with surprising accuracy. The average time of the recurrence was every 34 days, with 97.8%

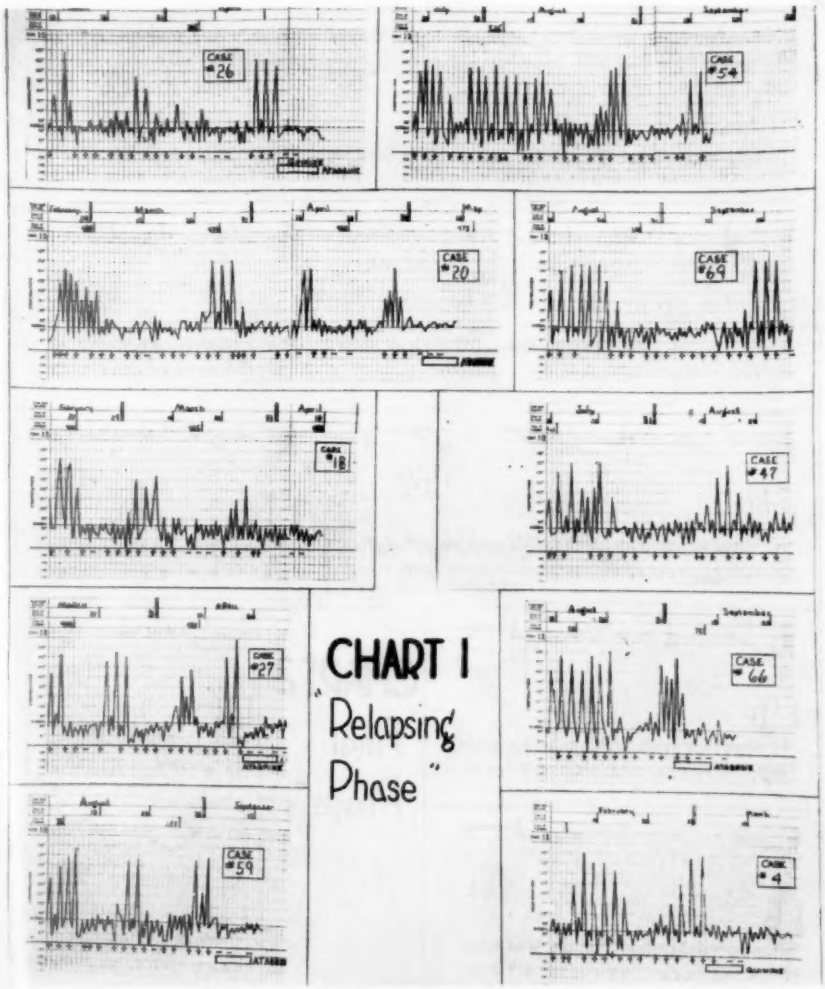


CHART 1

of all relapses occurring within 90 days. The remaining 2.2% of the relapses occurred between the 90th and 187th days. Actually, therefore, the pattern of relapsing Southwest Pacific malaria, with periodic relapses, is not characteristic of the natural course of the disease, but is characteristic of symptomatic drug therapy which produces only temporary clinical suppression.

As regards the total duration of the disease, it is evident that it may require 2 or more years to run its course once the phase of chronic relapse has become established, but it must be remembered that the cases we have studied may have had their clinical courses altered by previous therapy overseas. It cannot be positively stated that periodic drug therapy prolongs the course of the disease, but it certainly does not shorten it, and the studies which we have carried out strongly suggest that immunity and cure may come earlier if drug therapy is withheld. As a possible aid in determining this point, complement fixation tests for malaria were carried out weekly on the blood of these patients. However, the results

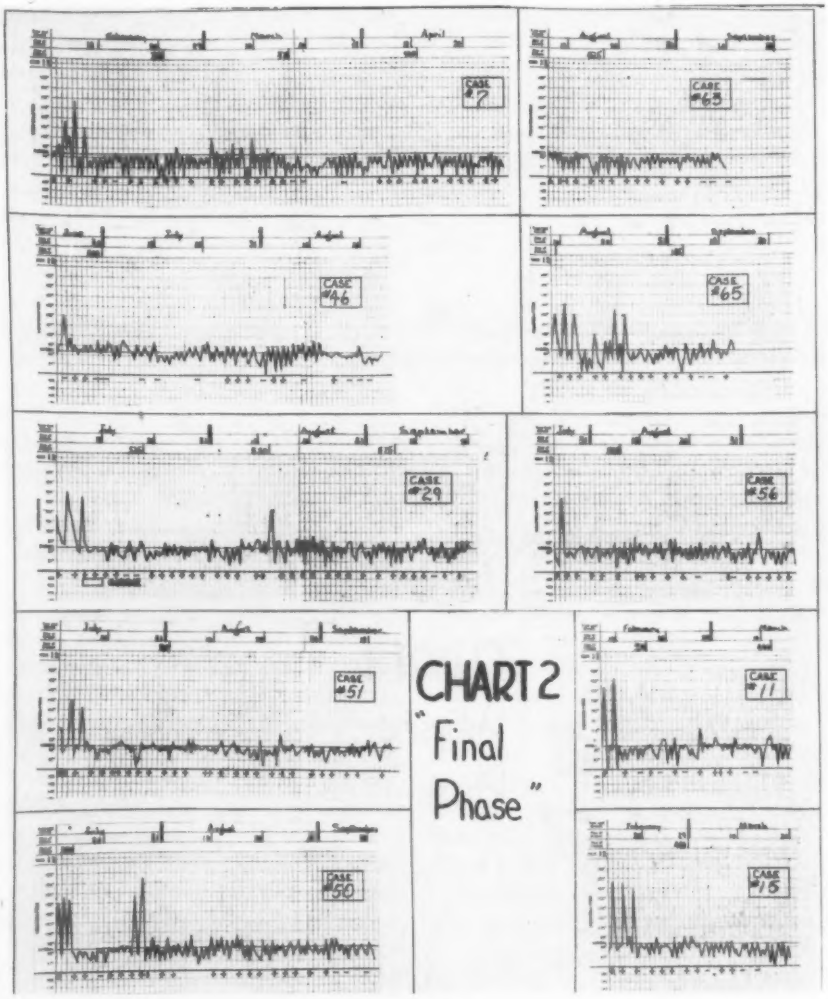


CHART 2

were too inconsistent to be a satisfactory guide in prognosticating either cure or subsequent relapse.

Whether or not the course of the disease would be greatly shortened by withholding therapy from the very onset could only be determined by initiating a program similar to ours overseas, and carrying out a prolonged follow-up study. The cases which have been continually suppressed clinically overseas by drug therapy and who first become ill after their return to this country when this drug has been withdrawn, may ultimately run the complete course of the disease as suppressive therapy may only have deferred the clinical onset, and not affected any reduction in its ultimate duration once it has started.

Summary. 1. The natural course of untreated chronic Southwest Pacific vivax malaria has been observed in 72 patients.

2. Our observations indicate that there are 3 phases of the disease: (1) an initial phase, characterized by irregular fever, often occurring daily; (2) an intermediate chronic relapsing phase, usually characterized by irregularly occurring "bouts" of fever, tertian in type, and parasitemia; and (3) a late or terminal phase which is subclinical and is characterized by irregularly appearing parasitemia.

3. As the development of immunity and presumably cure in chronic malaria apparently takes many months when drug therapy is withheld, "non-specific" therapy is an impracticable therapeutic procedure.

4. The frequently encountered cyclic periodicity of relapse in chronic Southwest Pacific malaria is apparently due to the drug therapy (atabrine) of the acute attack, and very rarely occurs without treatment.

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ELECTROCARDIOGRAPHIC EVIDENCE OF CARDIAC COMPLICATIONS IN INFECTIOUS MONONUCLEOSIS*

By Comdr. Willis F. Evans, (MC) USNR
and
Capt. Ashton Graybiel, (MC) USNR
U. S. NAVAL AIR STATION, PENSACOLA, FLORIDA

(From the Dispensary and the School of Aviation Medicine)

In the course of an epidemic of infectious mononucleosis in which upwards of 100 cases were observed, there were a few in which the heart apparently became involved. Our interest was first aroused when, during the clinical study of a patient presenting a problem in differential diagnosis, an electrocardiogram revealed T wave changes strongly suggesting pericardial involvement. This finding became of more than passing interest when it was later shown that the patient had infectious mononucleosis. Insofar as we are aware there have been few reports on infectious mononucleosis mentioning cardiac complications and none have included cases similar to those now to be described. The absence of fatal cases makes the problem impossible to study in autopsy material.

Case Reports. Case 1. W. R. P., a sailor 20 years of age, was admitted to the Dispensary on Oct. 3, 1944, complaining of fever and headache. Except for mild pleurisy at the age of 15, he had always been unusually well and robust until 2 days before admission when he developed the usual symptoms of grippe. At the time of entry, the body temperature was 99.4° F., the pulse rate was 60, and the respiratory rate was 20 a minute. Examination revealed no abnormality save for signs of nasopharyngitis. The heart was not enlarged, the sounds were of good quality, and no murmurs were heard. The blood pressure was 122 mm. Hg systolic and 76 diastolic.

He responded well to simple treatment for grippe until the 3rd day when his condition suddenly worsened. The temperature rose to 103.4° F. and the pulse rate to 96. The cervical and epitrochlear lymph glands were found to be enlarged. Examination of the blood revealed no anemia and the leucocyte count was 9650 (53% granulocytes, 46% lymphocytes, and 1% monocytes). Urinalysis was negative save for 1+ albumin.

On the 4th day there was pain in most of the large joints of the extremities and on the 5th day the joint pains were severe. A sparse, macular rash, confined to the trunk, appeared on this day and there was a nonproductive cough. Differential diagnosis included: (1) infectious mononucleosis, (2) endemic typhus, (3) cerebrospinal fever, and (4) rheumatic fever.

On the 7th day the patient was acutely ill, the temperature rising to 104.8° F., at which time the pulse rate was 96. He was mentally confused and there was moderate stiffness of the neck. There was no apparent change in heart size, the sounds were of good quality, and no murmurs were heard. The electrocardiogram showed low or diphasic T waves in all leads. There was no significant change in the blood findings. The sedimentation rate was 17 mm. in 1 hour. On the 9th day radiologic examination of the chest revealed no abnormality except that the heart was slightly larger than previously. Agglutination tests for endemic typhus, brucella abortus, and the typhoid group were negative.

The patient remained severely ill until the 13th day when he began to improve; the joint pains were less severe and the rash was fading. Radiologic examination still showed the heart to be enlarged and the electrocardiogram revealed slight inversion of the T waves in Leads I and IVF. On the 15th day the leucocyte count was 5900 with 68% lymphocytes, some of which were immature forms. The Paul-Bunnell test was positive in a dilution of 1:56.

The patient gained in strength and well-being, and on the 18th day was allowed out

* The views represented in this paper are those of the authors and do not necessarily reflect those of the Navy Department.

of bed. On this day the percentage of lymphocytes had risen to 74, with an increase in the number of immature forms, and the Paul-Bunnell test was positive in 1:224 dilution. The diagnosis of infectious mononucleosis now seemed certain. Convalescence was slow, but uninterrupted. On the 20th day radiologic examination showed that the heart had returned to its original size. The T waves in the electrocardiogram were still abnormally low in Leads I and II. The Paul-Bunnell test was positive in a dilution of 1:448, and remained so for a period of 3 weeks. He was returned to duty in good health Nov. 25, 1944, and was well and strong when last examined May 30, 1945.

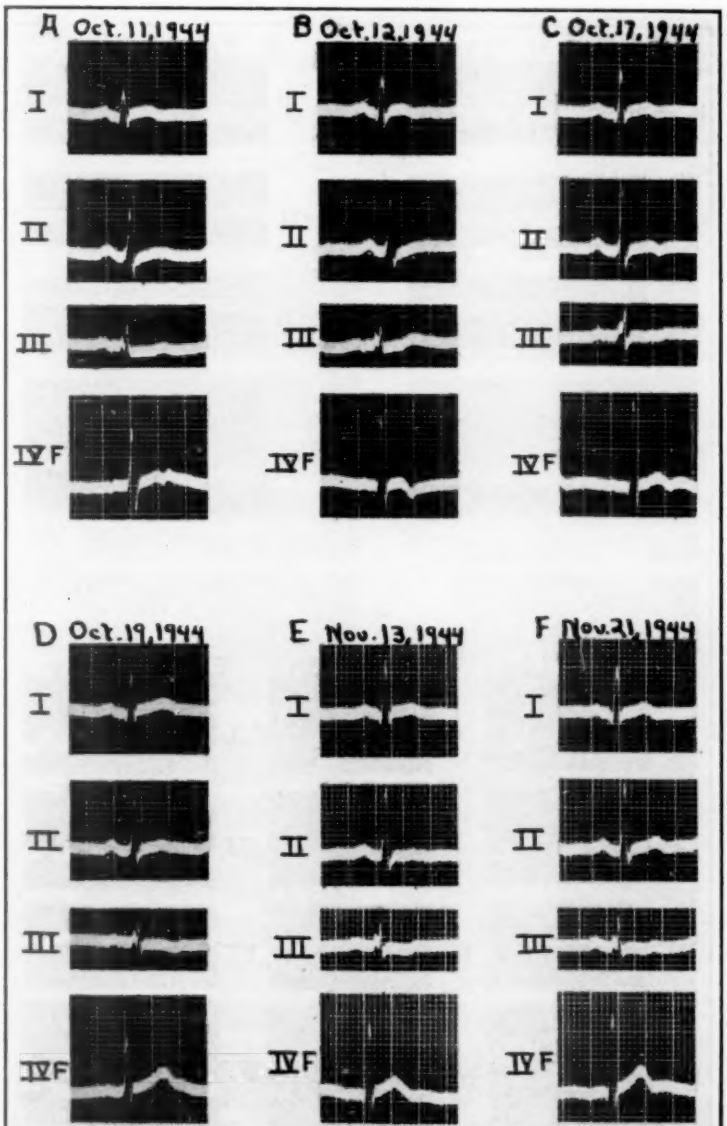

FIG. 1.—Showing serial electrocardiograms in the case of W. R. P. *A* shows low T waves in the limb leads and a notching of T in IVF. In *B* and *C* the T waves are low or inverted in all leads. In *D*, *E* and *F* there is a gradual return toward the normal.

A series of 22 electrocardiograms was taken throughout the period of illness and convalescence, and portions from 6 representative tracings are shown in Figure 1, *A-F*. There are changes in the amplitude of QRS, but the striking changes are the progressive lowering or inversion of the T waves in all leads with slow but eventual return toward the normal.

Case 2. J. L. T., a naval aviator 24 years of age, was active and well until Oct. 30, 1944, when he developed headache and malaise. Examination was essentially negative except for signs of nasopharyngitis. He did not respond favorably to symptomatic treatment and on the 3rd day was admitted to the Dispensary. The body temperature was 103.8° F., the pulse rate was 82, and

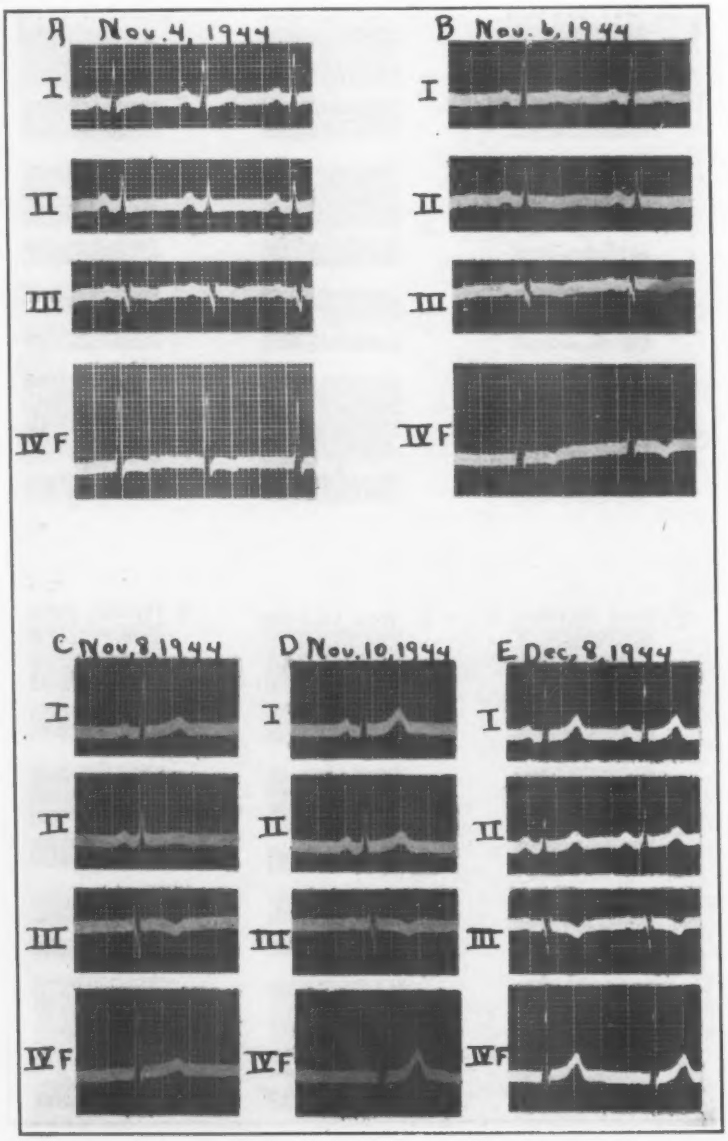

Fig. 2.—Showing serial electrocardiograms taken in the case of J. L. T. *A* was taken on the 5th day of illness and shows low or inverted T waves in all leads. The T waves remain low or inverted in *B*. *C*, *D* and *E* show a progressive return to the normal.

the respiratory rate 20. Examination revealed a very well developed person acutely ill. There were signs of inflammation of the nasopharynx, injection of the scleræ, and lacrimation. A sparse, maculo-erythematous rash was present over the trunk and thighs. There was moderate enlargement of the cervical lymph glands. The heart was not enlarged, the sounds were of good quality, and no murmurs were heard. The blood pressure was 126 mm. Hg systolic and 84 diastolic. The differential diagnosis included: (1) endemic typhus, (2) infectious mononucleosis, (3) measles, and (4) cerebrospinal fever. On the 4th day (2nd day of admission) the rash was extensive over the trunk and thighs. Examination of the blood revealed no anemia, the leucocyte count was 6400 (77% granulocytes, 22% lymphocytes, and 1% monocytes). Radiologic examination of the chest revealed no abnormality.

On the 5th day the patient complained of pain in the joints of the extremities, and tenderness of the muscles in forearms and calves. He was restless, nauseated, and mentally confused. The temperature was 102.4° F. and the pulse rate 80. The heart had not increased in size, but a slight friction rub was heard to the left of the sternum in the 4th interspace. An electrocardiogram taken on this day (Fig. 2, *A*) shows low or inverted T waves in all leads. Examination

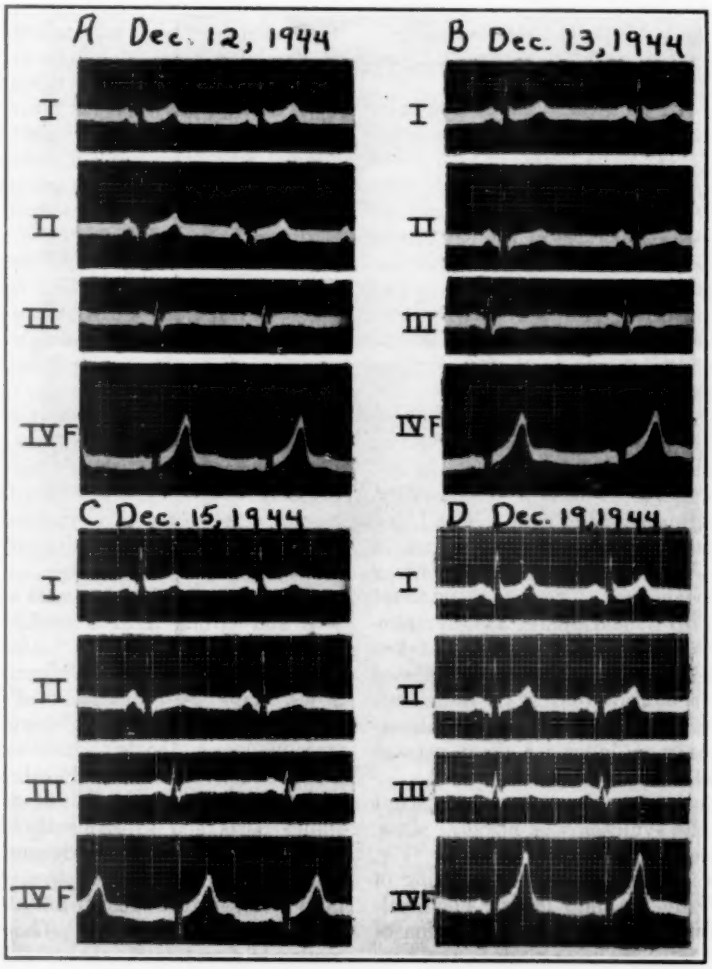

FIG. 3.—Showing electrocardiograms in the case of A. B. The electrocardiogram in A was taken on the 2nd day of illness and shows no definite abnormality. There is progressive lowering of T_1 and T_2 in *B* and *C* with a return to normal in *D*.

of the blood revealed no change except for the presence of a number of immature lymphocytes. The Paul-Bunnell test was positive in 1:112 dilution. A definite diagnosis was made of infectious mononucleosis, with involvement of the pericardium.

The patient remained severely ill until the 7th day, when he began to improve and subsequent recovery was uneventful. The rash and joint pains gradually disappeared, the temperature fell to normal, and the pulse rate decreased to 60. The Paul-Bunnell test became positive in a dilution of 1:224, and the percentage of lymphocytes increased to 45, with many immature forms. Serial electrocardiograms (Fig. 2, *A-E*) show a progressive change in the T waves from the abnormal to the normal. The patient returned to duty Nov. 21, 1944, feeling well. He was healthy and strong when last seen on May 26, 1945

Case 3. A. B., a chief petty officer 34 years of age, was admitted to the Dispensary on Dec. 11, 1944, complaining of pain in the chest. He had been in good health until 24 hours before admission when he noticed pain in the lower portion of the left lateral chest wall which was aggravated by respiration. Physical examination revealed a well developed person. The body temperature was 98.6° F., the pulse rate was 84, and the respiratory rate 15. Over the trunk there was a sparse, maculo-erythematous rash. The cervical lymph glands were enlarged. A few fine moist râles were heard over the base of the left lung. The heart was not enlarged, the sounds were of good quality, and no murmurs were heard. The blood pressure was 122 mm. Hg systolic and 78 diastolic. The examination of the blood revealed no anemia. The leucocyte count was 15,800 (61% neutrophils, 33% lymphocytes, and 6% eosinophils). Blood taken for a Paul-Bunnell test was later reported positive in a dilution of 1:224. Radiologic examination of the chest revealed no abnormality of heart or lungs. A diagnosis was made of infectious mononucleosis.

On the 3rd day there was no significant change in the symptoms or physical signs. An electrocardiogram taken this day (Fig. 3, *B*) shows slight but definite lowering of the T waves in the limb leads. The Paul-Bunnelt test was positive in a dilution of 1:896.

The subsequent clinical course was that of a mild illness. The fever was never greater than 100.6° F. (on the 6th day). The pulse rate ranged from 68 to 100. The rash began to fade on the 5th day and disappeared on the 7th day. Joint pains subsided with the rash. The highest percentage of lymphocytes was 51, with a moderate number of immature forms. Repeated radiologic examination of the heart and lungs revealed no abnormal findings. An electrocardiogram taken on the 4th day (Fig. 3, *C*) shows abnormally low T waves in Leads I and II, but a record obtained on the 8th day (Fig. 3, *D*) shows normal T waves.

Case 4. S. M. E., a naval aviator 23 years of age, entered the Dispensary June 5, 1945, complaining of headache and fatigue. Within the course of a few days he presented the characteristic clinical and laboratory findings of glandular fever. There was malaise, fever (103° F.), and generalized lymphadenopathy; the Paul-Bunnell test was positive in dilutions as high as 1:3584 and the blood smear showed 86% lymphocytes, some of which were immature forms. Examination of the heart revealed no abnormality except that the heart sounds heard at the mitral area decreased in intensity at the height of the illness. At no time was there rash or joint pains. Serial electrocardiograms were taken which show (Fig. 4, *A*, *B* and *C*) a progressive lowering of the T waves in Leads I, II, and IVF with gradual return to the normal.

In addition to the above 4 cases, there were a few others in which there were slight but definite electrocardiographic changes at the height of the illness. Also, there was 1 case of pericarditis with massive effusion in which the only etiologic diagnosis possible was infectious mononucleosis.

An aviation cadet, 20 years of age, was well and strong until 3 weeks previously when he first noticed a "catch" in the chest on taking a deep breath. Within a few days he complained of occasional twinges of pain radiating from the midsternum across the left chest and a slight non-productive cough developed. Three days prior to admission he was forced to discontinue sports and subsequently complained of malaise, anorexia, and dyspnea. At the time of examination, he appeared ill. The body temperature was 101.5° F. and the pulse rate 120 a minute. The heart was moderately enlarged, the sounds were of poor quality, and a friction rub was heard

in the 3rd and 4th intercostal spaces to the left of the sternum. The blood pressure was 150 mm. Hg systolic and 102 diastolic. There were no congestive phenomena. While the electrocardiogram was being recorded, the patient declared that he felt sick, and within a few seconds the radial pulse could not be felt. He responded to treatment for shock and was sent to the hospital with the diagnosis of pericarditis with effusion, possibly of rheumatic origin.

of coëxistent rheumatic fever was considered but thought to be unlikely since the onset was not preceded by a respiratory infection, the joints were never involved, the response to salicylates was unfavorable, and no cardiac murmurs were heard. Lacking positive evidence for any additional diagnosis, it was thought that the pericarditis was probably a complication of the infectious mononucleosis.

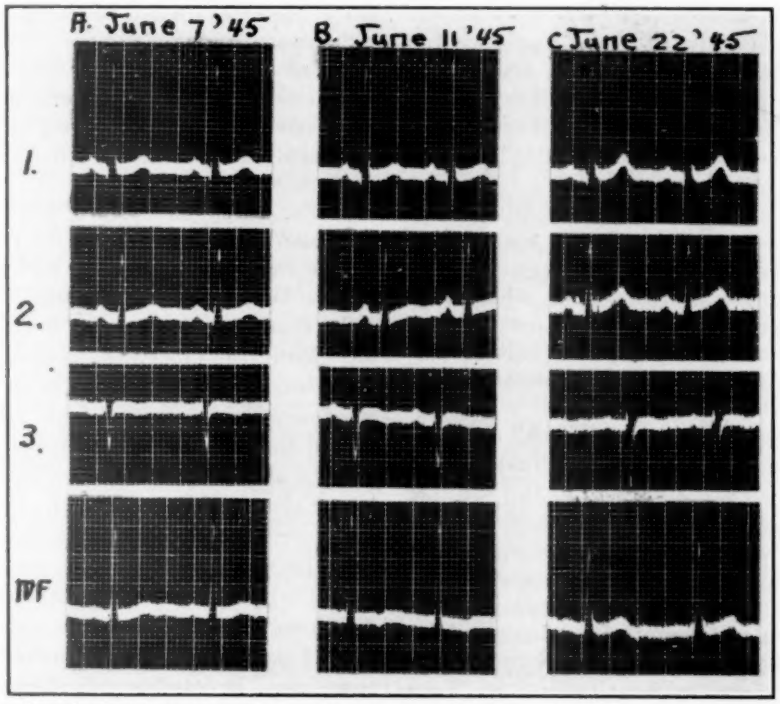

FIG. 4.—Showing serial electrocardiograms in the case of S. M. E. *A* and *B* were taken at the height of illness and show abnormally low or slightly inverted T waves in all leads. In *C*, the T waves are within normal limits.

We are indebted to Captain Jesshill Love, (MC) USNR, for information regarding the course of the patient's illness. Comprehensive studies, including examination and culture of pericardial fluid on several occasions, were undertaken in order to establish an etiologic diagnosis. The only definite finding was a positive Paul-Bunnell test in dilutions as high as 1:896. The percentage of lymphocytes increased from 21 to 59. The T waves of the electrocardiogram became moderately low in the limb leads and became diphasic in Lead IV F. The possibility

Discussion. The above 4 case reports are offered as proof that, in occasional patients with infectious mononucleosis, the heart may become affected. These patients presented the clinical and laboratory findings characteristic of infectious mononucleosis. It is of interest that in 3 of the 4 patients, involvement of the heart was detected shortly after the appearance of an erythematous rash and joint pains.

There is some evidence that the cardiac involvement was more of the pericardium

than of the myocardium. In Case 1, the T wave changes not only are characteristic of pericardial involvement but persisted over a longer period of time than would be expected if the myocardium alone was affected; long after the patient was apparently well, the T waves remained abnormally low in amplitude. In Case 2, a friction rub was heard and the T wave changes are consistent with pericarditis. In Case 3, the illness was not severe and it seems unlikely that the heart muscle was sufficiently affected to produce the electrocardiographic changes found. In Case 4, the only definite evidence of cardiac involvement was the electrocardiographic changes which resembled those in the other cases.

The heart rate was slow relative to the body temperature in Cases 1 and 2; there was evidence of central nervous system involvement in these cases which may have been a factor. In no instance was there evidence of congestive failure. The heart sounds in most cases remained good throughout the entire illness.

Bernstein,[1] in his monograph on infectious mononucleosis, states that cardiac disturbances are unusual in this disorder but that certain sequelæ have been reported which indicate that there may be involvement of the heart during an attack. This author refers to isolated reports[2,3] of valvular deformity following glandular fever and not only considers the possibility that rheumatic fever may have been present as a complication but that valvular injury may result in uncomplicated cases of infectious mononucleosis. The first named possibility was strongly considered in 2 of our cases early in the disease but there were good grounds for believing that rheumatic fever was never present.

Longcope[4] reported the appearance of ventricular extrasystoles in 1 of the patients of his series but observed no other electrocardiographic abnormalities. There were no cardiac arrhythmias observed in any of the cases studied by us.

Summary and Conclusions. 1. Four cases of infectious mononucleosis with cardiac complications have been presented. Additional cases are mentioned in which the same complications were possibly present.

2. The diagnosis of infectious mononucleosis was confirmed in each instance by the characteristic clinical and laboratory findings seen in this disease.

3. Rheumatic fever may have to be included in the differential diagnosis. In 3 patients, in addition to the usual symptomatology, an erythematous rash appeared associated with joint pains.

4. In all 4 cases there were alterations in the electrocardiogram; in 1, there was slight cardiac enlargement; and in 1 other, a friction rub was heard.

5. The evidence suggests that the cardiac involvement was mainly pericardial.

6. It is concluded that occasionally there may be cardiac complications in infectious mononucleosis.

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THE TREATMENT OF HUMAN HYPERTENSION WITH A KIDNEY EXTRACT*

By Charles D. Stevens, Ph.D.†
J. Harold Kotte, M.D.
Carl C. Smith, Ph.D.‡
and
Johnson McGuire, M.D.
Cincinnati, Ohio

(From the Cardiac Laboratory, Cincinnati General Hospital)

The treatment of hypertension with kidney extracts and the rationale of such therapy have been reviewed recently.[2,3,8] Favorable therapeutic results have been attributed respectively, to renin,[14] to angiotoninase (hypertensinase),[10] and to unspecified[6] or non-specific[12] factors present in these extracts. This paper reports the treatment of a small, carefully controlled series of hypertensive patients with a kidney extract which contained no renin or angiotoninase activity.

Kidney extracts were prepared by methods described in the literature[4,9] and were assayed in hypertensive rats and dogs. Modifications of these methods were made with a view to decreasing the toxicity and solids content of the extract without any considerable loss in blood pressure-lowering activity. In this way a concentrated extract was produced which assayed favorably in rats and dogs and was of relatively low toxicity. This extract was prepared in batches and pooled for treatment of a group of hypertensive patients.

Preparation of the Extract. Kidney extract was prepared from fresh hog kidneys which were minced with ice, treated with monoethanolamine, acidified with HCl, heated briefly,[9] and fractionated with ammonium sulfate. The material used was soluble in 3% trichloracetic acid from which it was precipitated by saturation with ammonium sulfate. The entire procedure, with the exception noted above, was carried out in the cold.

The 1700 ml. of extract (containing merthiolate 1:10,000) obtained from 725 lbs. of kidneys were pooled and stored in sterile vials in the refrigerator.

Fractionation of the extract was accomplished by first diluting with 7 volumes of water. The precipitate (fraction 1) was discarded. Ammonium sulfate was added to a final concentration of 30%. The resultant precipitate (fraction 2) was dissolved in water, dialyzed and concentrated. This material, containing merthiolate 1:10,000, is the fraction which was administered to Cases 1 and 3. Materials precipitated at 40 to 100% saturation with ammonium sulfate were combined as fraction 3.

Limitations of space preclude full presentation of the method.

Properties of the Extract. *Composition.* The extract was a slightly opalescent amber liquid which jellied in the refrigerator. It had a pH of 6.5 and a density of 1.01. It contained 5.9% solids, 0.98% total nitrogen ann 0.34% NPN (soluble in 5% trichloracetic acid) by Kjeldahl analysis.

Enzyme Content.§ The angiotonin activity of a standard angiotonin solution, assayed by injection into the abdominal aorta of normal rats,[5] was not diminished significantly following incubation with the extract in saline at pH 5 or 7. No renin activity (pressor response) was found on injection

* A preliminary report was presented at the 74th meeting of The Society of Clinical Surgery at Cincinnati, April 3, 1942.

† Present address: Biochemical Research Laboratory, Dow Chemical Company, Midland, Michigan.

‡ Present address: Institute of Medical Research, Christ Hospital, Cincinnati, Ohio.

§ Dr. Page kindly confirmed the absence of angiotoninase and renin activity from our extract while Dr. Kemp of his laboratory confirmed the blood pressure-lowering activity of the extract in hypertensive rats.

of the extract intravenously into normal dogs and rats, though doses of 2 ml. per kg. gave small transient reductions in blood pressure in anesthetized hypertensive dogs. No amylase, proteolytic, or lipolytic activities were found in the extract.

Toxicity. Intravenous injection of 15 ml. of extract/kg. body weight in rabbits, 20 ml./kg. in mice, and 3 ml./kg. in a monkey produced no noticeable reactions. Intravenous injections in hypertensive (silk) rats lowered their blood pressures (tail cuff technique) and raised their rectal temperatures.

Ten mice, 10 rats, 10 guinea pigs and 5 rabbits were given intramuscular injections of 0.2 ml./kg. daily for 37 days. Equal numbers of animals were similarly injected with distilled water. Sections of heart, liver, spleen, pancreas, kidney and other tissues showed no more pathologic change than the controls. Anaphylactic reaction in guinea pigs could be produced by the extract but was not elicited by the series of 37 daily injections.

Forty patients seen regularly in the Allergy Clinic were given intradermal injections of the extract, which elicited no positive reactions.

times by 2 different observers; many readings were taken at each visit and 3-day running averages have been charted in the accompanying illustrations. Patients were given the routine hospital diet without restriction of salt. No sedatives were given.

Daily treatment was prolonged until no favorable response was being obtained, or until reactions necessitated stopping the extract.

Case Histories. Case 1. B. G. (Fig. 1) was a 50 year old colored female, who was first told she had an elevated blood pressure in 1934. In 1936, her blood pressure ranged from 230–200/140–120. With limitation of activity she improved somewhat.

When admitted for treatment with extract she had slight cardiac enlargement, hypertensive retinopathy (Grade 3), ECG evidence of left ventricular strain, normal urinary dilution-concentration range, and normal BUN. Urea clearance, 70% of normal, remained unchanged during treatment. Retrograde pyelograms showed no abnormalities. After 14 days in the hospital, kidney extract was administered for 28 days. On the 28th hospital day urticaria and a generalized erythematous rash with itching were

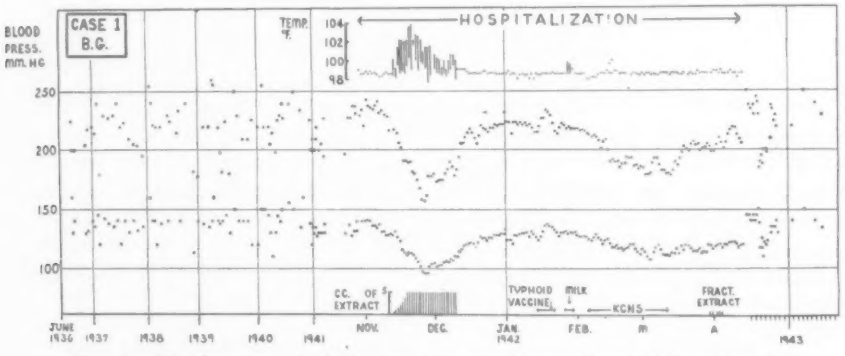

Fig. 1.—Blood pressure, body temperature and therapeutic schedule of Case 1.

Clinical Trial. The extract was administered to 4 hypertensive patients; 3 had been under observation for long periods; a fourth, with malignant hypertension, was selected because some reports noted striking improvement in cases of this type.

Patients were hospitalized on the Medical Service of the Cincinnati General Hospital for 14 to 26 days before treatment was begun. Blood pressure readings were taken twice daily after 1 hour bed rest at appointed

first observed. On the 42nd hospital day local reactions became so pronounced that treatment was discontinued.

On the 45th day the patient's serum gave a positive precipitin test with a 1:1000 dilution of whole extract. By the 63rd day the titer had declined to 1:5 and was the same on the 148th day. The second fraction of the original extract, for which the patient had no precipitins, was given for 6 days

beginning on the 152nd day; no reactions were noted.

Case 2. E. H. (Fig. 2), a 46 year old white female, a known hypertensive since 1938, was admitted to Cincinnati General Hospital in 1940 because of hypertensive encephalopathy. A bilateral lumbar splanchnicectomy was done. Her blood pressure showed no significant change after operation, although some symptoms were improved.

Case 3.—R. S. (Fig. 3), a 27 year old colored female, was first found to have hypertension in 1939. On admission in 1942 she had slight enlargement of the left ventricle and her eyegrounds showed mild arterial constriction. The ECG, dilution-concentration, urea clearance and pyelograms were normal. On the 26th hospital day kidney extract* was begun. Mild urticaria and angioneurotic edema were noted on the

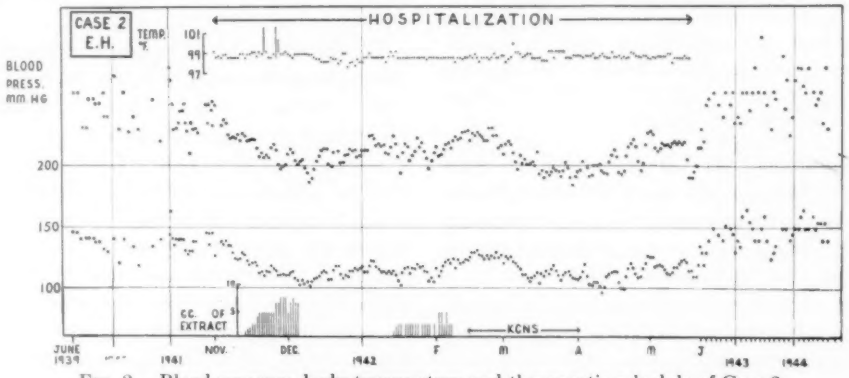

Fig. 2.—Blood pressure, body temperature and therapeutic schedule of Case 2.

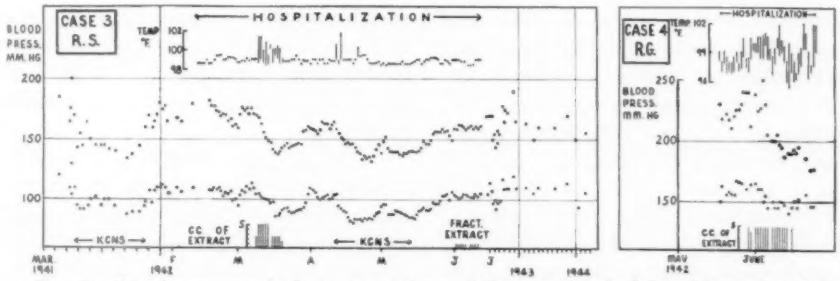

Fig. 3.—Blood pressures, body temperatures and therapeutic schedules of Cases 3 and 4.

On admission in 1941, examination showed moderate cardiac enlargement, evidence of diffuse cerebral vascular disease, hypertensive retinopathy (Grade 3), normal PSP and dilution-concentration tests. Her urea clearance, 40% of normal, remained fixed during treatment. Intravenous pyelograms were normal. Kidney extract was begun on the 14th hospital day and stopped on the 36th hospital day because of poor response. During this period there was no appreciable change in her physical state. Six weeks later, skin tests with the whole extract were still negative, and the same extract was again injected without affecting her symptomatology.

34th hospital day; increase in these symptoms necessitated discontinuation of the injections. On the 35th and 43rd hospital days the patient's serum gave a positive precipitin test with a 1:5 dilution of the whole extract. On the 122nd day the precipitin titer was 1:10.

Beginning on the 111th hospital day she was treated with the second fraction of kidney extract to which she gave no reaction on intradermal injection. No effects were noted.

Case 4.—R. G. (Fig. 3), a 36 year old colored female, first noted progressive exertional dyspnea 4 mos. prior to hospitalization. Orthopnea, paroxysmal nocturnal

dyspnea, and mild ankle edema appeared about 2 weeks before entering the hospital.

Examination on admission disclosed papilledema, retinal hemorrhages and exudate, and marked arteriolar constriction. Findings of congestive failure were present. Albumin, many pus cells, and small numbers of casts were found in the urine. The BUN rose from 33 to 150 mg. % during hospitalization.

Extract was started on the 12th hospital day and continued for 16 days. Progressive weakness, Cheyne-Stokes respiration, increasing edema, and delirium were observed during this time. The patient died in uremic coma on the 40th hospital day.

Summary of Clinical Observations. *Blood Pressure.* All 4 patients showed some fall in blood pressure following treatment with kidney extract as indicated in the accompanying graphs. This was more striking in the systolic than in the diastolic level. The change in blood pressure was undoubtedly associated with the use of kidney extract, with the possible exception of Case 4.

Symptoms. All patients complained of various symptoms associated with hypertension, most of which remained unchanged during hospitalization.

Fundus Oculi. No significant retinal changes were noted during the hospital period.

Toxic Reactions. Remittent fever was the most commonly observed toxic reaction. Injections of the extract were given in the morning and the temperature peaks followed in the late afternoon. Lethargy and anorexia accompanied the markedly febrile periods. Slight leukocytosis was observed in 1 case (R. S.), and 2 patients showed a slight weight loss during the treatment period.

Skin tests and allergic history of each patient were initially negative. Despite this, 2 subjects developed urticaria and mild angioneurotic edema on the 10th and 15th days of treatment, which disappeared in a few days although treatment was not stopped.

Local reactions, consisting of pain and heat and redness of the skin overlying the injected area were observed to a varying degree in each case. In 2 subjects (B. G., R. S.) their severity necessitated discontinuation of treatment.

The fall in blood pressure during thiocyanate administration[7] was of the same magnitude as that following kidney extract in 2 cases (R. S., E. H.) but was not as marked in the other patient. Thiocyanate did not induce the febrile response seen during kidney extract injections.

Discussion. The method of preparing this kidney extract, while similar to published methods,[4,9,11,12] differs from them in several respects, including an initial alkaline extraction and a final precipitation with trichloracetic acid. Alkalies help dissolve kidney tissue and monoethanolamine was particularly useful in this respect. Trichloracetic acid removed renin, angiotoninase and other enzymes.

Some investigators have suggested that renin or angiotoninase is responsible for the blood pressure lowering activity of kidney extracts. While a fall in blood pressure may accompany injection of these enzymes it may also occur in their absence as shown by our results. It remains to be seen whether these enzymes are active in pure form.

It has also been suggested that the blood pressure lowering activity of kidney extracts arises from their pyrogenic activity, as in the case of pyrogenic insulin, tyrosinase, typhoid vaccine, etc. Since the depressor effect in our patients appeared coincident with fever, the fall in blood pressure might be attributed to the elevated temperature, although blood pressure measurements made during the afternoon peak of the fever were not appreciably lower than those made in the morning before the temperature began to rise. This is at least suggestive that vasodilatation alone was not responsible for the depressor effect. Other unknown factors, possibly renal hyperemia as suggested by Chasis *et al.*,[1] may be operative in producing this effect.

It is possible that allergic or toxic effects played some part in the lowering of the

blood pressure. Although reactions were never observed immediately after injection, various allergic phenomena (local reactions and urticaria) appeared later in 2 subjects, coincident with the greatest fall in blood pressures. The reactions we observed were similar to the initial mild reactions described by Schales, Stead and Warren.[12]

There is an interesting possible correlation between development of serum precipitins and the clinical effectiveness of the extract which suggests that more intensive study of this aspect may be desirable. Cases 1 and 3 had the most pronounced fall in blood pressure, and this fall coincided with the theoretical onset of maximum antibody production. This is confirmed insofar as precipitin tests were made. Furthermore, the non-antigenic fractions administered in Cases 1 and 3 had no effect. No precipitin tests were done with serum from Case 3 whose skin tests were uniformly negative.

Our subjects did not exhibit a favorable symptomatic response such as others have reported. No appreciably objective change was observed in the eyegrounds or in cardiac or renal function. No decrease in the hemoglobin level, similar to that reported by Page *et al.*[10] was observed, although our cases were treated for considerably shorter periods.

Conclusions. 1. The preparation and properties of a kidney extract used in the treatment of human and animal hypertension are reported. This extract contained no demonstrable angiotoninase or renin and was of relatively low toxicity in animals.

2. Four hypertensive patients were treated parenterally with this extract. Three of them showed during treatment a noteworthy fall in blood pressure, associated with fever. The fourth patient who developed little fever, demonstrated only a slight depressor effect.

3. The 2 subjects who demonstrated the greatest fall in blood pressure exhibited hypersensitivity reactions and developed serum precipitins.

4. The results obtained with this kidney extract in the treatment in human hypertension do not recommend its use. Until the toxic effects of such kidney extracts can be eliminated, their therapeutic evaluation will be difficult and the mechanism of their action undetermined.

Details of the preparation of the kidney extract and case histories are available on request to the authors.

Dr. Virgil Hauenstein and Dr. Arthur Freedman of the Cardiac Laboratory assisted with the clinical aspects of the work. Dr. A. G. Wedum of the Dept. of Bacteriology performed the precipitin tests. Dr. P. M. Zeek of the Dept. of Pathology performed the pathologic examinations. Mr. Henry Block and Miss Lucille Keifer assisted with certain chemical analyses. Dr. Irvine Page furnished the angiotonin solution. Various amines were supplied by Carbide and Carbon Chemicals Corporation.

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I. S. RAVDIN, B.S., M.D.
HARRISON PROFESSOR OF SURGERY, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PENNSYLVANIA
AND
C. G. JOHNSTON, M.S., M.D.
PROFESSOR OF SURGERY, WAYNE UNIVERSITY, DETROIT, MICHIGAN

A REVIEW OF THE PRESENT CONCEPTS ON FLUID BALANCE

By William E. Abbott, M.D.
DETROIT, MICHIGAN

(From the Department of Surgery, Wayne University College of Medicine, and The Detroit Receiving Hospital)

The purpose of this paper is briefly to review the present concept of fluid, electrolyte and protein metabolism in the normal and diseased individual, and to emphasize some of the more recent impressions on this subject.

The intake and output of fluid and salt in adults has been well discussed by Peters,[60] and by Coller and Maddock;[15] it is summarized in Figure 1. Butler and Talbot[12] have more recently reviewed the use of parenteral fluids and have stressed the difference in the daily requirements for infants, adolescents and adults. It can be seen from the numerals in parentheses in this diagram that the output of salt and water can be greatly accelerated in such conditions as vomiting, diarrhea, external fistulas, excessive perspiration, etc. Approximately 8200 cc. of fluid having an electrolyte make-up somewhat similar to plasma are normally excreted into the gastro-intestinal tract per day.[30] When the usual daily intake of 2500 cc. is added to this it is apparent that large quantities of fluid pass through the gastro-intestinal tract each 24 hours. If an obstruction or loss of interstitial fluid due to vomiting, diarrhea or external drainage occurs, the absorption of water and salts is retarded or prevented and it can be readily understood how dehydration may thus occur quite rapidly.

A composite diagram on the available information[30,60,63,64] of the amount and distribution of body fluid is shown in Table 1. It should be noted that the plasma volume constitutes a relatively small portion of the total body water, but since in the normal individual exchange of fluid in the body tissues occurs quite rapidly,[26] the plasma volume is kept at a fairly constant amount.

The movement of fluid is not only rapid and continuous in and out of the gastro-intestinal tract and to and from the circulatory system, but also through the other body tissues and the kidney. It is well accepted that approximately 170 liters of water can pass through the glomeruli of a normal individual each day and that about 169 liters of this fluid is reabsorbed.[25,69] It has also been shown that the colloidal substances of the plasma (albumin, globulin, etc.) leave the vascular system fairly rapidly.[50,55] Apparently

much of the plasma protein leaving the circulatory system in normal individuals is lost through the liver capillaries, since McCarrell, Thayer and Drinker[50] found that the concentration of protein in the lymph from the liver is practically identical with that of plasma.

crease there is a reciprocal rise of the other ion. When excessive amounts of sodium are lost,[62] as might occur in patients with intestinal obstruction or intubation, an external fistula, or diarrhea, the plasma bicarbonate concentration is reduced by an intracellular shift of bicarbonate and

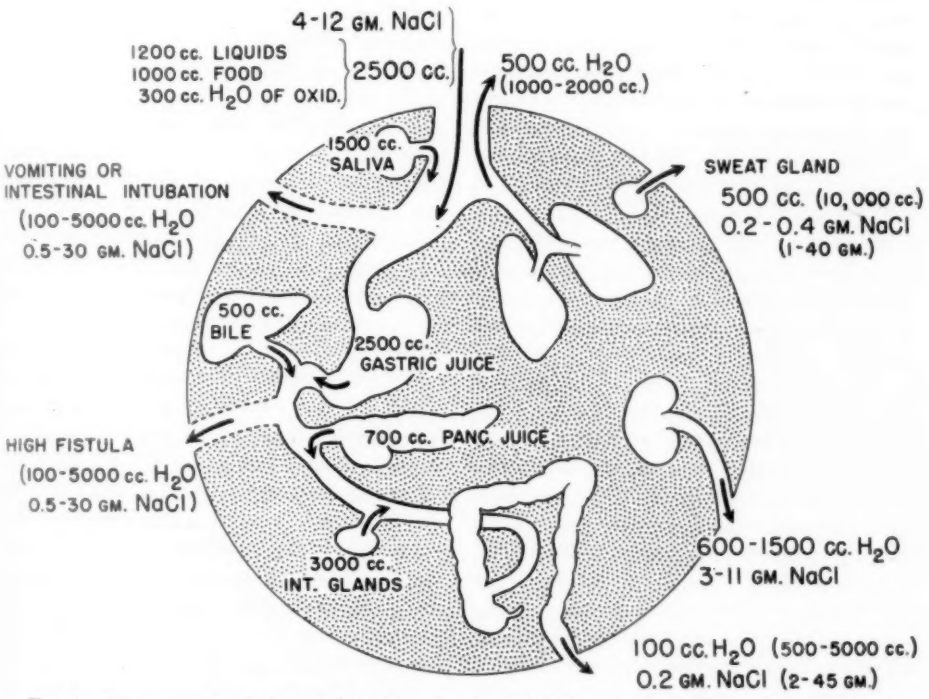

FIG. 1.—The normal and abnormal intake and output of fluid and salt. (The possible abnormal loss of fluid and salt is shown in parenthesis.)

TABLE 1.—THE APPROXIMATE AMOUNT AND DIVISION OF THE BODY FLUID

Normal body fluid compartments	Body weight (%)	154 lb. or 70 kg. man (cc.)
Extracellular:		
Plasma	4–5	3,000
Interstitial	12–18	11,000
Intracellular	40–50	35,000
Total body water, approx.	70	49,000

The importance of sodium and potassium in maintaining a relatively constant amount and distribution of the body fluids has been stressed.[17,30,31,59,60,64] It has been shown[30,38,59,60] that the osmotic effect of the anions in the extracellular fluid is not as significant as that of the cations, since when either chloride or bicarbonate de-

the removal of larger amounts of carbon dioxide through the lungs.[72] If an excess of chloride is present, part of it may pass into the cells or it is eliminated through the kidneys.[30,60,72] When dehydration is mild, the body gives up water to the kidneys in an attempt to maintain a normal electrolyte pattern; but, as the state

of dehydration becomes more marked, water can no longer be spared in adequate amounts for the formation of urine, so a distortion of the chemical anatomy of the body fluids occurs, usually with a resulting acidosis or alkalosis.[30,37,59] It is at this stage, when dehydration is fairly marked, that an insufficient amount of water is available to excrete the nitrogenous waste products (prerenal azotemia).[25,48,59] As a result of this, the nonprotein nitrogen or blood urea concentration increases. Marriott[47] well emphasized the alterations that occur in dehydrated patients and pointed out that if the condition progresses, kidney damage eventually occurs. Very often the urine contains albumin, casts and cells, and after rehydration the kidneys frequently are unable to concentrate urine in a normal fashion. Since the catabolic phase[32,34,47] is often accelerated when dehydration is present and the kidney function reduced, it may be necessary to force fluids (4000 to 5000 cc. orally or intravenously in the form of 5% dextrose in distilled water with 50 to 100 gm. of amino acids per day) so that the urine volume can be raised sufficiently (2000 to 3000 cc. daily) in order that the kidney may eliminate the acumulated waste products.[1] The giving of adequate sugar and protein seems advisable since the protein stores are being depleted, and the caloric intake derived from dextrose and amino acid solution is usually adequate to stop or to minimize the catabolic process. Amino acid solutions should be given in moderate amounts even though the non-protein nitrogen concentration is elevated, since such cases are usually in a state of negative nitrogen balance.

It has been shown that so far as total body water is concerned, the osmotic effect of the plasma proteins and cell proteins is practically negligible.[70,73] Thus the state of total body hydration is largely dependent on the presence of sodium and potassium. Starling,[70] and later Krogh[41] and Landis,[44,45] demonstrated that the size of the plasma volume in the normal individual is apparently largely dependent on the amount of plasma protein present. In the diseased state, however, such is usually not the case. In such disorders, when plasma protein is given, it may have only a very transient effect on the blood volume.

In burned patients[6,27] and animals,[5,58,68] it has been shown that by giving a physiologic salt solution orally or by injecting it into the burned area,[8] the tissue tension is apparently increased to a point where the loss of fluid from the circulation is minimized and the absorption of it from the traumatized area is enhanced. From other studies,[21,24,54] it has been noted that even though the colloid osmotic pressure has been greatly increased, fluid will not be drawn back into the circulation as long as an extracellular depletion of salt and water exists. It has been pointed out repeatedly[2,44,59,70] that the size of the plasma volume in the normal or diseased patient is not dependent on the protein concentration alone, but is governed by the following factors: (1) the total solute concentration of the extracellular fluid volume and the available water, (2) the osmotic pressure of the interstitial fluid, and (3) the blood filtration pressure minus the tissue tension. It has been demonstrated that the normal exchange of body fluid may be affected because the capillary permeability is increased (due to drugs, inflammation or anoxia)[40,56,57] or because of endocrine or renal dysfunction (causing a failure of the kidneys to excrete water and salt in a normal fashion).

It was formerly believed that the sodium and potassium ions were largely confined to their specific body fluid compartments. However, more recent studies have shown[18] that under some circumstances such is not the case. Darrow and Engel[18] have demonstrated that in experimental hemorrhagic shock and in anoxia, there is an appreciable intracellular increase in the sodium ion and a decrease in potassium within the liver. Hence, while under certain circumstances osmotic equilibrium between the intracellular and

extracellular phases may occur because of the transfer of electrolytes, this is probably the exception rather than the rule.[16] More commonly, osmotic equality is established following the transfer of water, rather than electrolytes, after alterations in the solute concentration.[16,30,61] Such changes were demonstrated experimentally by Darrow and Yannet[19] and later confirmed by other workers.[38,54] Thus, when there is a reduction of the extracellular electrolyte (especially sodium) there is an intracellular shift of fluid and more recently the reverse has been demonstrated[74] (*i. e.*, when the solute concentration of the extracellular phase is increased there is a shift of fluid from within the cell to the extracellular fluid compartment with a resulting intracellular dehydration). As Gamble[30] points out, this exchange of fluid occurs normally in relatively small amounts, but if the shift of fluid is large, the plasma volume may be seriously depleted,[53,54] or intracellular dehydration may occur with serious consequences.[77] Decreases in the total extracellular electrolytes and fluid may occur in gastric or intestinal intubation, vomiting, diarrhea, drainage from external fistulas, etc.;[17,62] increases are usually noted following the giving of large amounts of a physiologic solution of sodium chloride,[13,74] and in edematous states[75] (pregnancy, cardiac and renal edema). Peters[62] clearly demonstrated why patients with an obstruction of the gastro-intestinal tract who are treated by gastric or high intestinal intubation should be denied water and food by mouth while such therapy is being employed. If some oral intake seems desirable, they should be given relatively small amounts of an isotonic salt solution. To permit water or food by mouth, except in some instances of low intestinal intubation, usually accelerates the excretion of gastric, pancreatic and intestinal juices, increases the likelihood of distention and thirst and thus makes the control of the patient from the acid-base and fluid balance standpoint a more difficult one. In fact, it may produce a condition resembling the one that the patient is being treated for.

In considering the methods for giving parenteral fluids it should be recalled that when a solution of 5% dextrose in distilled water is given subcutaneously or intraperitoneally, it causes a temporary extracellular fluid dehydration. It has been shown experimentally[19,54,79] that sodium and other solutes pass into the area of the injected fluid faster than the glucose and water diffuse out. This temporarily depletes the solutes in the extracellular phase and in order to restore osmotic equality there is an intracellular shift of water. In a patient who is well hydrated, the effect is slight, but when dehydration is present the added decrease of the plasma volume may cause a marked diminution in the blood pressure.

In the above discussion it is emphasized that in certain instances there is an inability on the part of the kidneys to excrete salt and water normally. This may occur in cases of trauma[9] or burns,[6,51] infection,[43,76] anoxia,[7] cardiac[28] or endocrine[42] disorders, and following anesthesia.[10,67] This fact should be kept in mind when fluids are being ordered for such cases. The undesirable effects of an excessive saline administration has been stressed,[3,13,14,15,23,49,71] and of course should be avoided.

Following earlier work on dehydration[29,30,31] it was felt that the plasma volume was maintained in a relatively constant state at the expense of the interstitial fluid until the patient's condition had become critical. It was believed that the plasma volume decreased only after a marked depletion of the interstitial fluid volume had occurred. However, more recent work has shown[4,53] that while the interstitial fluid compartment may supply water to the plasma volume, both phases of the extracellular compartment decrease simultaneously during dehydration.

During the past decade many methods and "clinical rules" have been introduced and advocated[15,20,22,35,39,66,78,80] in the hope

of finding a simple way of controlling the fluid, protein and salt needs. Unfortunately, previous work[47,52,65] which pointed out the failure of solute concentrations to mirror the state of hydration was largely overlooked, and it has recently again been emphasized that such methods are usually inadequate.[1,3,4,6,11,13,43] Figure 2 presents in a simplified form the impressions gained recently and demonstrates how the cell volume and protein concentration may be misleading. The upper column in Figure 2 represents the normal findings and the lower columns show the changes that may occur in dehydration and overhydration. Since a high, normal, or low plasma protein concentration may be obtained in a patient when a decrease in the total circulating protein is present and a normal or low concentration found in states of overhydration when there is an increase or decrease in the circulating protein, the plasma protein concentration in itself frequently fails to offer any assistance in judging the state of hydration or nutrition. Because of the fairly wide deviation of the normal cell volume,[33] and the withdrawal or destruction of cells in shock[35] and dehydration[47] the hematocrit may also be misleading.

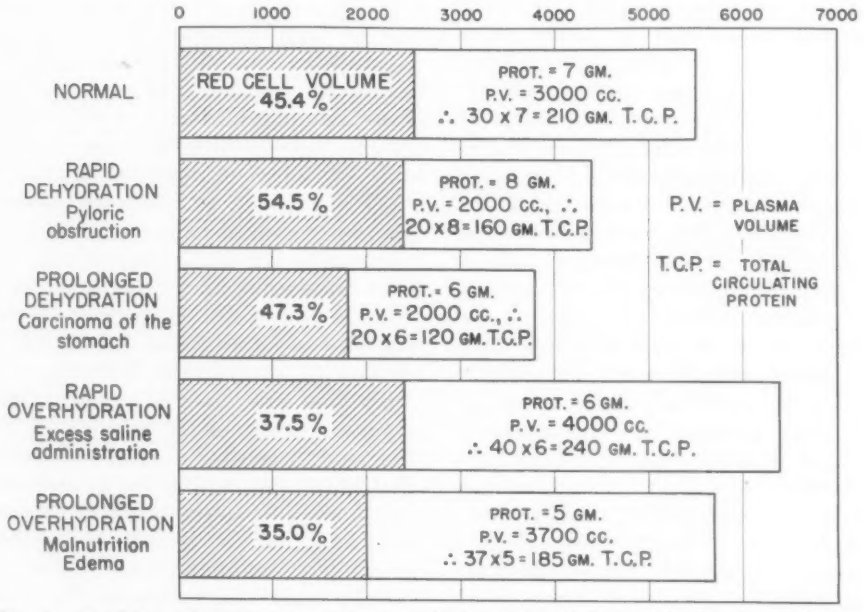

FIG. 2.—The failure of the plasma protein concentration to denote the need for therapy, or the amount of total circulating plasma protein present. (The cross-hatched area equals the red cell mass, and the open area of the bar the extent of the plasma volume.)

TABLE 2.—THE FAILURE OF THE PLASMA CHLORIDE LEVEL TO DENOTE THE TOTAL AMOUNT OF EXTRACELLULAR CHLORIDE

Type of case	Plasma chloride (conc. meq./L.	Extracellular fluid (cc.)	Total meq. of chloride in the extracellular fluid
Normal	105	14,000	1470
Pancreatic, biliary or high intestinal fistula	118	10,000	1180
Pyloric obstruction	88	10,000	880
Malnutrition, burn, and cardiac edema	88	20,000	1760

Table 2 demonstrates the fallacy of employing the plasma chloride level. These figures are theoretical but are based on the findings taken from experimental

and clinical studies.[1,4,52] It should be noted that high, normal or low values may occur in dehydration and that excessive amounts of extracellular fluid chloride may be present when normal or low concentrations exist.

Figure 3 demonstrates some of the more common changes in the blood chemical concentrations that may occur. Such studies may aid greatly in determining a decrease in the solute concentration (Fig. 4, marked dehydration) may take place when a state of dehydration exists. A decrease in the solute concentrations, while not shown in Figure 4, can also occur in states of overhydration.

Thus, it becomes important to think in terms of total body water and salt rather than solute concentrations alone, since changes in the volume and concentration

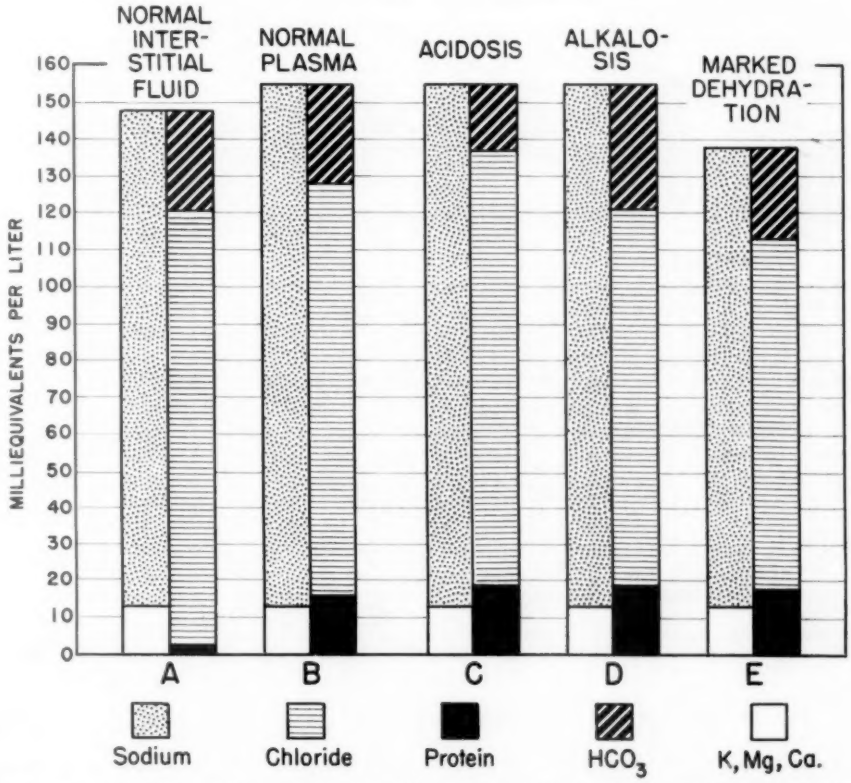

FIG. 3.—The composition of the normal extracellular fluid (*A* and *B*) and the possible structural changes that may occur in the plasma during disease (*C*, *D*, *E*).

the acid-base balance, but in themselves do not permit quantitative conclusions to be drawn on the state of hydration. Figure 4 was included in order to help in visualizing the alterations in concentration and volume that might occur in such cases. It can be seen that an increase or a decrease in the total amount of water or salt may occur with little change in concentration, and it is also evident that can occur in numerous different ways. Elaborate studies to determine the state of fluid balance often are of little value since the control volume cannot be estimated accurately[33] and the state of hydration can be determined fairly well from a careful history and physical examination. Changes in hydration can usually be demonstrated in the course of a physical examination (eyeball tension, condition of

tongue, elasticity of the skin, etc.) and an estimate of the severity of the disorder may be made by a careful history (type, severity and duration of illness), and by observations of the response of the patient to therapy (changes in the amount and in the specific gravity of urine, in the turgor of the skin, in mental alertness, and in the weight and thirst of the individual in question).

The importance of these obvious and easily discernible findings ought not be underestimated in the evaluation and treatment of dehydration or overhydration. Often too much reliance is placed on single or even repeated isolated determinations of concentration of substances in the blood, especially chloride and protein. To be of value such data must be considered in relation to the general state of nutrition and hydration of the patient as indicated by the history, the physical examination, and the volume and specific gravity of the urine.

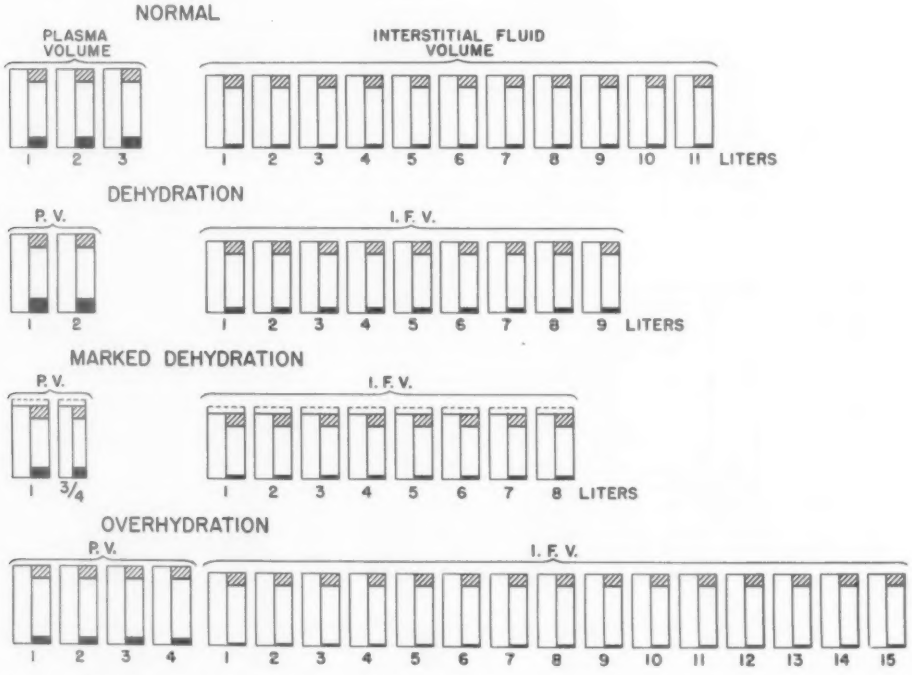
NORMAL
PLASMA VOLUME
INTERSTITIAL FLUID VOLUME
1 2 3
1 2 3 4 5 6 7 8 9 10 11 LITERS
DEHYDRATION
P. V.
I. F. V.
1 2
1 2 3 4 5 6 7 8 9 LITERS
MARKED DEHYDRATION
P. V.
I. F. V.
1 3/4
1 2 3 4 5 6 7 8 LITERS
OVERHYDRATION
P. V.
I. F. V.
1 2 3 4
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

FIG. 4.—Changes in the extracellular fluid volume (concentration changes may occur as shown in Figure 3 but also volume alteration should be taken into consideration).

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OPHTHALMOLOGY

UNDER THE CHARGE OF
WILLIAM L. BENEDICT, M.D.
HEAD OF THE SECTION OF OPHTHALMOLOGY, MAYO CLINIC, ROCHESTER, MINNESOTA
AND
H. P. WAGENER, M. D.
ASSISTANT PROFESSOR OF OPHTHALMOLOGY, MAYO FOUNDATION, ROCHESTER, MINNESOTA

RETINAL LESIONS IN ACUTE DISSEMINATE LUPUS ERYTHEMATOSUS

By H. P. Wagener, M.D.

In many cases of "fever of undetermined origin," before the clinical syndrome is sufficiently well developed to permit a definite diagnosis, ophthalmoscopic examination of the ocular fundus is made in the hope of finding in the optic disk, the retina, or the choroid some clue to the nature of the systemic disease. In a few of the diseases which might fall into this category, such as subacute bacterial endocarditis and miliary tuberculosis, the ophthalmoscopically visible lesions are recognized to be sufficiently characteristic to warrant a fairly accurate diagnosis. In others, such as disseminate lupus erythematosus, Libman-Sachs disease, and periarteritis nodosa, however, no definitely diagnostic fundus lesions have been described as yet. Among patients with acute disseminate lupus erythematosus, lesions in the retina occur rather frequently. It seems possible that, from more universal studies of the retina in these cases with more accurate descriptions of the nature and course of the lesions, a reasonably characteristic and diagnostic ophthalmoscopic picture might evolve.

Unfortunately, much of the available data on the retinal lesions in this disease is to be found only in rather brief notes of fundus examinations in reports of individual cases. Some of these notes are rather vague. Thus Guion and Adams[7] state that in 1 of their patients "retinitis" had been observed by a previous examiner. Another of their patients had "postneuritic optic atrophy." Only a few reports of histologic studies of the eyes have been presented. Yet, among the case reports, there can be found descriptions of retinal lesions characteristic of, or associated with, the toxic, inflammatory, vascular, and embolic features of the systemic disease.

In 1935, Pillat[16] reported his ophthalmoscopic observations in 48 cases of chronic lupus erythematosus. In 16 cases, he found isolated lesions in the choroid which resembled healed tuberculous choroiditis. In 3 of these patients there was an acute exacerbation of the lupus. In 2 of the 3, Pillat found additional foci of acute choroiditis which he believed were characteristically tuberculous. He presented his observations as evidence in favor of the tuberculous etiology of lupus erythematosus. Keil[8] expressed the opinion that the lesions described by Pillat might well be tubercles in the choroid but that they were most probably incidental findings and not a manifestation of systemic lupus. Previous to this, in 1929, Bergmeister[3] had described lesions which he interpreted as metastatic tubercles in the retina in a patient with acute disseminate lupus erythematosus in whom necropsy revealed disseminated tuberculosis. In the right eye, the disk was hyperemic and there were irregular white patches along the retinal veins. In the left eye, there were many "cotton wool" exudates and there were a number of small white dots in the macula. The eyes were not examined histologically.

Undoubtedly, the lesions described by Bergmeister are those seen most commonly in cases of acute disseminate lupus

erythematosus. However, as has been demonstrated by the histologic studies of Maumenee,[16] Bergmeister misinterpreted their nature. In 1922, Keith and Rowntree[9] reported on their studies of the renal complications in 4 cases of this disease. In one of their patients the fundi were normal at the initial examination. However, 1 month before the patient's death, 2 cotton wool patches were observed in the retina. During the following 2 weeks, more of these patches developed; so that, at the last examination, 12 were present in the right retina and 6 in the left. In the main, these cotton wool patches tend to develop in the terminal phases of the disease. However, they are not necessarily a fatal prognostic sign, since they may appear during an acute exacerbation from which the patient may recover, at least temporarily. In 1935, Baehr, Klemperer, and Schifrin[2] reported their findings in 23 cases of acute disseminate lupus. They stated that lesions were present in the ocular fundi of 12. They mentioned the presence of fluffy exudates but they called attention also to perivascular hemorrhages and they noted circumpapillary edema in 2 cases. In the discussion of their paper, Longcope[14] stated that he had observed in 1 case marked swelling of the optic disk during an acute exacerbation of the eruption and, in another, swelling of the disk, hemorrhages and small exudates which disappeared coincident with temporary disappearance of the rash and subsidence of the fever.

Kurz,[12] in 1938, was probably the first to demonstrate the true histology of these white patches in the retina. In a case which he observed 1 month before death, he noted 4 or 5 white patches, varying in size from $\frac{1}{4}$ to $\frac{1}{2}$ disk diameter, in the macular retina superficial to the retinal vessels. The disks were normal. A few small hemorrhages were present in the retina. Histologic examination of the eyes obtained at necropsy demonstrated that the white patches consisted of varicose hypertrophy or ganglioform degeneration of nerve fibers (cytoid bodies). Kurz thought the lesions in his case were identical with the retinitis septica of Roth and considered them to be of toxic and not bacterial embolic origin. He made no mention of lesions in the retinal vessels.

Essentially similar ophthalmoscopic findings have been reported by Rose and Pillsbury,[17] Keil,[8] Maumenee,[15] Stickney and Keith,[19] and Cluxton and Krause.[4] It would be difficult to say whether the small light spots described by Abramowicz and Dulewicz[1] represented edema residues or were actually only hyaline deposits in the lamina vitrea of the choroid. Hemorrhages and exudates were present in the retinas of 3 of the 4 cases reported by Cluxton and Krause.[4] The optic disks were normal. The authors did not advance any definite theory as to the origin of these lesions. They said: "The lesions are not necessarily associated with renal disease because the blood pressure is usually normal, nor are they related to bacterial embolic phenomena because the blood cultures are for the most part sterile." "The evidence points to the lesions being local in origin and representing but one of the manifestations of a systemic disease." Rose and Pillsbury[17] stated that intraocular lesions were common and included papilledema, sometimes with extension of the edema into and beneath the retina, retinal detachment and atrophy, guttate retinitis, perivascular exudates and hemorrhages, and choroidal degeneration. They expressed the opinion that these lesions were a part of the widespread vascular disease. The vascular lesions as described by Baehr, Klemperer and Schifrin[2] include: (1) capillary dilatation with extravasation of blood and serum; (2) proliferative endothelial vascular lesions with thrombus formation; and (3) degenerative or necrotizing lesions in the walls of capillaries, arterioles and venules, often with hemorrhages into adjacent tissues.

Keil[8] also thought that the lesions in the retina were of vascular origin. He stated: "In systemic lupus erythematosus, the fundi often reveal alterations. The

evidence appears to indicate that these changes arise primarily in relation to the blood vessels." He observed that the hemorrhages and the soft fluffy exudates were arranged in general in perivascular fashion and he thought that the exudates were probably simply collections of edematous fluid similar to that in the upper part of the corium skin. He did not regard the lesions as pathognomonic of lupus erythematosus and was not able to correlate them precisely with the severity of the clinical course of the disease though he did regard them as definite evidence that the disease had become systemic. Keil called attention to his personal observations of peripapillary edema of varying severity and expressed the opinion that this lesion occurred more commonly than was generally suspected. He thought that this transudation of edema fluid into the peripapillary retina was the result of vascular damage in the retina and was not due to an increase in intracranial pressure. Baehr, Klemperer and Schifrin[2] also expressed the opinion that the lesions in the retina were not due to hypertension but were analogous probably to the lesions observed on the fingers, primary vascular alterations with hemorrhagic extravasations and perivascular exudation. The involved skin around the nail bed of the fingers was seen to contain many more patent and dilated capillaries than normal with extravasation of serum and red cells into the subcutaneous tissues. Stokes, Beerman and Ingraham[20] state: "As the discoid type of lesion is expressive of local cutaneous infection-allergy of the follicular inflammatory type with atrophy, so the acute disseminate type is the clinical type of lupus erythematosus with multiform disseminated cutaneous and systemic lesions resulting from allergic inflammation of the vascular system." "The vasculoallergic type of 'lupus erythematosus' then, may be preponderantly local and cutaneous in its manifestations, or preponderantly systemic—fever, lymphadenopathy, leukopenia, absolute or relative, with or without thrombocytopenia, and with demonstrable vascular lesions of the eyes, kidney and endocardium."

The theory that this type of retinopathy is of vascular origin lacks histologic support. In 1940, Maumenee[15] reported the results of ophthalmoscopic and histologic studies of the eyes of 4 patients with acute disseminate lupus erythematosus and of 1 patient with chronic disseminate lupus erythematosus. In his opinion, the lesions found were to be regarded as a manifestation of generalized toxemia. He described the following 3 typical lesions: (1) Small, fluffy, yellowish white to white spots located in the superficial layers of the retina, never larger than the disk, usually in the posterior part of the fundus, and very similar in appearance to the cotton wool patches of hypertensive retinopathy. These patches were present in all cases. Histologically they were shown to be areas of cytoid bodies. (2) Small hemorrhages placed superficially in the retina and not located in relation to the white patches nor to the larger retinal vessels. These were observed ophthalmoscopically in 3 cases and were found microscopically in the nerve fiber layer of the retina. (3) Slight papilledema. This was observed ophthalmoscopically in 3 cases and was confirmed histologically in 2. In 1 case, there was noted ophthalmoscopically slight generalized blurring of the choroidal reflex which was thought to indicate subretinal edema. Histologic examination in this case revealed serous exudation and hemorrhages in the stroma of the choroid in an area of about 2 or 3 disk diameters around the optic nerve. The choroidal vessels showed moderate hyaline degeneration of the intima and proliferation of the adventitia. In this same case there was slight hyaline degeneration of the intima of the retinal arterioles typical of arteriolar sclerosis. The blood pressure was 140/90. In the other 4 cases the vessels were normal.

In addition to the above findings, Maumenee noted histologically in all the cases a slight round cell infiltration of the choroid similar to the "septic choroiditis"

described by Friedenwald and Rones.[5] This was not detected ophthalmoscopically. Ophthalmoscopically visible lesions of apparently similar histologic type were described by Semon and Wolff[18] in a case of acute disseminate lupus erythematosus. They observed in each fundus round white elevated lesions resembling tubercles of the choroid. One of these was located underneath a retinal vein. Histologic examination revealed a fairly generalized invasion of the choroid with inflammatory cells. At the site of one of the ophthalmoscopically observed lesions there was well-marked subretinal exudate containing inflammatory cells (lymphocytes, a few neutrophils and a few large mononuclears), some pigment, some spindle cells, and capillary vessels (granulation tissue). There was no evidence of tuberculosis. The retina was normal. Lesions of this type may be considered possibly as manifestations of the chronic infections, frequently streptococcic, which may be a factor in the etiology of the disease.

In my experience, the type of toxic retinopathy described by Maumenee[15] is the type of lesion encountered most frequently in patients with acute disseminate lupus erythematosus. Instances of gross organic involvement of the retinal vessels are much less common. Klauder and Ellis[10] described in 1 patient various sized, irregular, fluffy, cloud-like patches and a few small hemorrhages scattered through the retinas particularly around the disks. This description would suggest the ordinary type of toxic retinopathy. However, the patient improved under treatment with gold sodium thiosulphate and, 1 year and 3 months after the original observation, the "exudative retinitis" had disappeared. There was slight pallor of the disks. Some of the larger retinal vessels were "replaced by scar tissue" and the other vessels showed varying degrees of sclerosis and a corkscrew appearance. There was collateral circulation on the disks. The vision which had been 3/60 originally was now 6/60. In the discussion of this case, Lillie interpreted the lesions as diffuse perivasculitis and periphlebitis associated with pallor of the disks and the formation of new blood vessels on and around the disks.

Goldstein and Wexler[6] described bilateral secondary optic atrophy (post-neuritic) in a fatal case which was diagnosed clinically as acute disseminate lupus but in which necropsy did not reveal confirmatory evidence of this disease. Ophthalmoscopically, both optic disks were pearly white with serrated edges. The retinal arteries and veins were extremely narrow. There was some periarterial sheathing. Scattered throughout the posterior parts of the fundi were numerous discrete punched-out areas of retinal atrophy bordered by a fringe of pigment, always located in relation to a retinal vessel. Histologic examination revealed atrophy and gliosis of the optic nerves with the preservation, however, of many normal blood vessels. There was atrophy of the walls of the larger arterioles in the retina with constriction of the lumen and degeneration of the media which was replaced by almost acellular fibrillar or homogeneous material staining faintly with eosin and resembling hyaline. In some places there was present in addition a perivascular fibrosis so extensive as to produce discrete areas of atrophy of the retina with compact fibrous tissue replacement. The choroid was not involved.

At a recent meeting of the American Ophthalmological Society, Koch and McGuire[11] described somewhat similar findings in a case diagnosed clinically as acute disseminate lupus erythematosus. Necropsy was not obtained. Ophthalmoscopic examination revealed periarteritis and periphlebitis with hemorrhage and exudation into the retina. The lesions gradually became more extensive with involvement of more vessels. Subsequently some of the vessel branches were apparently fibrosed and obliterated and pallor of the optic disks developed.

In view of the rather frequent occurrence of vegetative endocarditis in cases of acute disseminate lupus erythematosus, it is rather surprising that embolic phe-

nomena are not observed more often in the retina. Keil[8] mentions that he had seen a case with blindness (in 1 eye?) which was attributed to an "embolism" of the central artery of the retina with secondary glaucoma. Keil was inclined to blame the occurrence of the embolism on an injection of gold. Recently I had the opportunity of observing a young girl in whom the clinical diagnosis of acute disseminate lupus erythematosus was confirmed at necropsy. Vegetations were found on the heart valves (non-bacterial). About a month before her death, there was an area of ischemic edema in 1 retina associated with closure, probably embolic, of a small terminal arteriole. A few days before her death, a number of petechial hemorrhages with white centers were present in each retina.

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PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF DECEMBER 18, 1945

The Effect of the Alkyl Sulfates on Gastric Secretion in the Rat. H. Shay, M.D., S. A. Komarov, M.D., Ph.D., H. Siplet, B.S., and M. Gruenstein (Medical Research Laboratory, Samuel S. Fels Fund). Adequately starved Wistar-strain white rats grown in our own colony were anesthetized with ether and intracecal urethane. The pylorus was tied, avoiding damage to any blood vessels. The esophagus was exposed in the neck and a loose ligature was placed around it. The stomach was then lavaged through a stomach catheter with 4 cc. of warm normal saline. The stomach was emptied completely and 2 cc. of the test solution was introduced. The esophageal ligature was tied as the stomach catheter was removed. The esophagus was cut proximal to the ligature and its proximal end was sutured to the skin by a submucous suture. The abdominal and neck incisions were then closed. Half of the animals in each group received atropine (25 mg. per 100 gm.) subcutaneously as the operation was started.

They recovered rapidly from their anesthesia. Six hours after the gastric instillation of the test solution they were sacrificed and the gastric contents collected, measured and analyzed for pH, free and total acid, chlorides, pepsin and mucin.

The test solutions included distilled water, 0.1%, 0.5% and 2% solutions of a very pure sodium dodecyl sulfate dissolved in distilled water. In the 8 groups of 8 to 11 animals each, the results within each group were sufficiently uniform to justify the following conclusions:

Resorption may occur in the rat's stomach. This capacity was especially evident in the atropinized group in which the mean rate of absorption following the instillation of distilled water was 0.13 cc. per hour per 100 gm. body weight.

When sodium dodecyl sulfate was in contact with the gastric mucosa it exerted a stimulating effect upon the gastric secretory mechanism, the nature of which was related to the concentration of the solution. With 0.1% and 0.5% solutions all secretory elements—the parietal, peptic and mucus secreting cells—are strongly stimulated. The 2% solution exerts a selective effect in that only the mucus secreting cells are stimulated. The stimulating effect of the sodium dodecyl sulfate becomes progressively stronger with the increase in concentration from 0.1% to 2%. From a comparison of the results in the atropinized and non-atropinized animal, it becomes clear that stimulation of the parietal and peptic cells by the weak solutions is entirely a reflex effect through the vagus, while the stimulation of the mucus secreting cells in all concentrations was a twofold action—partly reflex through the vagus and in part a direct action upon the mucus secreting cells.

A Study of the Influence of Various Dietary Deficiencies on the Response of Mice to the Virus of Poliomyelitis. J. H. Jones, Ph.D., C. Foster and W. Henle, M.D. (Depts. of Physiol. Chem. and Pediatrics, Univ. of Penna. and Children's Hosp.). In a previous report[1] it was shown that either a dietary deficiency of vitamin B_1 or partial starvation of animals on a complete diet increased the resistance of mice to the murine adapted strain of poliomyelitis virus. Similar observations have been made by Rasmussen *et al.*[2] By use of the paired feeding technique it was subsequently demonstrated[3] that the vitamin deficiency exhibited a greater protection than did the

restriction of food intake, indicating that the effect of the vitamin deficiency could not be entirely due to the inanition.

Following these observations the effect of several other deficiencies on the response of mice to the virus of poliomyelitis has been studied. These deficiencies have included that of the B_2 complex, B_6, protein, and tryptophane. In each case the animals were continued on the deficient diet until fairly marked deficiency symptoms were manifest. They were then inoculated intracerebrally with an amount of virus that would produce paralysis and death in about 80% of the animals on a complete diet. In the case of each of the above deficiencies total deaths were 80% or more within 28 days after inoculation when the experiments were discontinued. The incidence of paralysis varied from above 50% to above 80%. Some of the deaths were due to the deficiencies as indicated by numerous deaths in corresponding groups on deficient diets but injected with a suspension of uninfected brain. There was no conclusive evidence that any of the above deficiencies (vitamin B_2 complex, vitamin B_6, protein or tryptophane) either increased or decreased the resistance of mice to the virus of poliomyelitis.

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Observations on an Oligodynamic Action of Copper on Human Erythrocytes. M. H. Jacobs, Ph.D., and D. R. Stewart, Ph.D. (Dept. of Physiology, Univ. of Penna.). The striking effect of traces of copper in decreasing the permeability of human erythrocytes to glycerol reported by Jacobs and Corson in 1934 has been studied more quantitatively by improved methods. It has been found that in a 0.3 M solution of glycerol lightly buffered at pH 6.5, an easily detectable copper effect may be produced by a concentration of copper chloride of 8×10^{-8} M and a 90% decrease of permeability to glycerol by one of 6.4×10^{-7} M. Several lines of evidence indicate that the copper effect, which is readily reversible, is confined to the surface of the cell. Calculation shows that under the conditions of these experiments, at the higher of the 2 concentrations mentioned, there might be available for combination with each cell a maximum of 30 million copper atoms; these could cover only a little more than 1% of its surface. Actually the amount of copper taken up by an erythrocyte must be much less than this, since after exposing a glycerol-copper solution to one lot of cells, which are then quickly removed, its effect on a fresh lot of cells may be only slightly diminished. In 1 such experiment with an initial copper concentration of 6×10^{-7} M it is estimated that each of the first lot of cells could have removed at most 1 million copper atoms which could have covered no more than about $\frac{1}{2000}$ of the total cell surface. Because such a minute fraction of the surface may be involved in a relatively enormous permeability effect, and because this effect is limited to certain kinds of erythrocytes already known to be exceptionally permeable to glycerol, it is tentatively concluded that such cells must possess some special mechanism, of restricted distribution in the cell surface, which in some way facilitates the entrance of glycerol and which is reversibly inhibited by very low concentrations of copper.

The Action Potential of Human Nerve and Muscle, Normally and After Nerve Injury. M. G. Larrabee, Ph.D., and R. Hodes, Ph.D. (Johnson Foundation, Univ. of Penna.)* *Nerve Action Potentials.* In an attempt to obtain an early prognosis after nerve injury, action potentials were recorded from 31 injured nerves during operative exposure for exploration, neurolysis, or removal of tantalum cuffs.

* Work done under a contract, recommended by the Committee on Medical Research, with the Office of Scientific Research and Development.

For comparison the action potentials were measured in 9 normal nerves, or above the point of injury in regenerating nerves. The normal potentials were all larger than any found in the regenerating portion of a nerve. Technical difficulties, mostly incidental to the necessity of recording from small regenerating fibers in large nerve trunks in continuity, prevented satisfactory observation in about one-third of the injured nerves. In at least 7 other instances no action potential could be detected although the sensations of the patient (under local anesthesia) or the contraction of muscles clearly indicated the presence of functional fibers. It was therefore concluded that technical difficulties plus limitations in sensitivity render the method unsatisfactory for detecting the presence of a small number of functional fibers in a large nerve, and hence of doubtful usefulness for prognosis.

Electromyograms. Muscle action potentials in response to supramaximal percutaneous stimulation of various nerves were recorded in a number of normal individuals and in patients with peripheral nerve injuries. The potentials were recorded through small electrodes on the skin. Suitable electrodes and supports were devised for recording from all the major muscle groups in the hand, forearm, leg, and foot. Control observations were made to determine the limitations of the method, particularly those due to the wide spread of the action potential of each muscle. Decrease in amplitude of the action potential after nerve injury indicates decrease in the number of muscle fibers innervated, while increase in latency of the response indicates slowing of the conduction velocity of the regenerating nerve fibers and therefore a decrease in axonal diameter.

The normal conduction velocities in the median and ulnar nerve fibers supplying the hand muscles and in tibial and peroneal nerve fibers to the foot muscles ranged from 44 to 65 meters per second. After nerve suture and sometimes after spontaneous recovery of nerve function, the velocities were much lower, being accurately measured at less than 50% of normal in some cases and estimated to be as low as 5% to 10% of normal in others. Velocity appears to increase progressively during the 1st year after suture, but probably never regains more than 60% of normal. Since velocity is known to be directly proportional to the diameter of an axon, this implies a similar limitation in axonal growth after suture. In contrast, fibers of approximately normal diameter rapidly develop in many cases where regeneration occurs without nerve surgery.

The amplitude of action potential recorded from a given normal muscle is variable (average difference between duplicate determinations = 23%), and in addition the average amplitude is different for different muscles. In examining muscles whose nerves have been injured, we have routinely expressed the amplitude of the maximal response as a per cent of the maximal action potential of the same muscle in the uninjured extremity of the same individual. After nerve suture muscle action potentials in response to nerve stimulation were first detectable at a time which depended on the distance from lesion to muscle, indicating rates of regeneration in good agreement with the commonly accepted values of 1 to 2 mm. per day. In general, re-innervation could be detected by watching for movement during a voluntary effort of the patient before an action potential could be recognized. For the later stages of recovery, it is convenient to plot the per cent of normal action potential amplitude against the number of months allowed for recovery divided by the distance from the lesion to the muscle. Against this abscissa, recovery was found to occur at more or less comparable rates in various sutured nerves. In comparison those nerves which did not require operation recovered their function at a wide variety of speeds, often much more rapidly than after the most favorable suture. By comparison with data such as this, it should be possible to tell whether recovery

is lagging unduly in any peripheral nerve patient submitted to similar electromyographic examination. It cannot yet be regarded as established, however, that the method adds enough to the usual clinical examination to justify its extensive adoption, except in cases of hysteria or malingering where the normality of the peripheral nerve and muscle can be definitively demonstrated.

BOOK REVIEWS AND NOTICES

RORSCHACH'S TEST. II. A Variety of Personality Pictures. By SAMUEL J. BECK, PH.D., Head of Psychology Laboratory, Department of Neuropsychiatry, Michael Reese Hospital, Chicago; Associate Professor of Psychology, Northwestern University. Foreword by ROY R. DRINKER, LT. COL., M.C. Pp. 402. New York: Grune & Stratton, 1945. Price, $5.00.

THE purpose of the first volume was to demonstrate the process used in evaluating Rorschach test processes. The present volume is concerned with interpretation: analyses of Rorschach records of certain persons who must remain anonymous. The chapters of Part I are: Concerning Personality, and Psychological Significance of Rorschach Test Factors. Those of Part II are: The Intelligence Curve, The Adolescent Years, Schizophrenic Solutions, Neurotic Struggles, and Before and After: The Tests Repeated in the Same Persons. Beginning with the record and interpretation of an important university president and foremost scientist, the studies include a nurse in training, a mother-son struggle, hebephrenia in an adolescent boy, reaction and recovery in an ex-soldier, a male overt homosexual, together with other important personality pictures.

A principal objection to the Rorschach test has been its tediousness but no satisfactory short-cut has yet been devised. The group method which the writer continues to omit was introduced by Harrower-Erickson in 1941, and has been employed with sufficient promise of success to justify its continuance. In this procedure the blot pictures are projected onto a screen where they are viewed by classes of from 20 to 50 subjects. Certain objections have been raised, some of which are: the responses must be written, each subject receives the same amount of time, handling of the cards is lacking, etc. Subjects who may be unsuited to this method should receive the routine questioning test. Less important workers have sought to improve the originators technique, but not this exponent—he continues to hew to the line. Through wide experience, a sympathetic and understanding treatment, the writer has given us a book of high merit.

N. Y.

THE PHYSIOLOGY OF THE NEWBORN INFANT. By CLEMENT A. SMITH, M.D., Professor of Pediatrics, Wayne University College of Medicine, Medical Director, The Children's Hospital of Michigan. Pp. 312. Springfield, Ill.: Thomas, 1945. Price, $5.50.

CONVERSION from intra- to extra-uterine living throws a great strain upon the human infant, at a moment when the organs and their functionings are remote from the stability of adult development. A detailed and scholarly concentrate of what is known concerning the observable facets of this conversion is here presented, filtered and crystallized by the critical mind of an author whose contributions to this field are eminent in their own right.

Successive chapters deal with respiration; circulation; blood; liver function; metabolism and heat regulation; digestion; nutrition; renal excretion; endocrinology; immunology. There are informing summaries of prenatal energy metabolism, intra-uterine respiratory movements, and fetal circulation, and of the adjustments these make to worldly living. Controversial problems receive logical appraisal.

The book is more of a reference than a text. Pediatricians, obstetricians, and other physicians who are discontented with merely conforming to simple rule-of-thumb routines in the care of newborns and prematures will find it an authoritative mine of knowledge and inspiration.

I. W.

MEDICAL CLINICS OF NORTH AMERICA. Boston Number. Specific Methods of Treatment. Pp. 1341. Phila.: Saunders, 1945. Price, $16.00 a year.

THIS issue is a timely summary of specific methods of treatment. With the recent

advances in specific therapy it becomes increasingly more difficult for the busy practitioner to keep abreast with these developments. This issue gives a concise appraisal of some of these newer advances.

Janeway, Berenberg and Hutchin's Clinic on "Indications and Uses of Blood, Blood Derivatives and Blood Substitutes" is well written, concise, and very informative, as is also the Davies Clinic on "The Treatment of Meningitis." In all this issue is a valuable contribution. J. F.

WHAT THE INFORMED CITIZEN NEEDS TO KNOW. Edited by BRUCE BLIVEN and A. G. MEZERIK. Pp. 377. New York: Duell, Sloan & Pearce, 1945. Price, $3.00

THE Table of Contents of this timely and wide-embracing book suffices to show why a notice of it is not unsuitable for medical among other citizens.

The United Nations Charter (E. Stettinius, Jr.); America and World Trade (W. Berge); World Industrialization (M. Cooke); Our Relations with Russia (W. Batt); The Inter-American Family (S. Inman); Relief and Rehabilitation (E. Thomas); Jobs for All (H. Wallace); The Threat of Inflation (C. Bowles); Patients and Monopolies (J. O'Mahoney); War Surplus—Tool for Peace (A. Mezerik); Planning, Liberty, and Security (A. Hansen); Science and the American Future (B. Bliven); Rivers and Prosperity (L. Hill); Health is Everybody's Business (T. Parran); Good Houses for Everybody (C. Abrams); Tax Policy for a Prosperous America (R. Paul); The Family-Size Farm (J. Patton); Veterans: The Twelve-Million-Man Question (C. Bolte); The Problem of Minorities (C. McWilliams); Which Way Politics? (I. Brant); Labor's New Responsibilities (Philip Murray). E. K.

URANIUM AND ATOMIC POWER. By JACK DE MENT, Research Chemist, The Mineralogist Laboratories, and H. C. DAKE, Editor, The Mineralogist Magazine. With Appendix on the Atomic Bomb. Pp. 335. Brooklyn: Chemical Publishing Co., 1945. Price, $4.00.

THE release and harnessing of atomic energy has become of such immediate practical importance to everyone—the medical man, scientists in general, and the man on the street—that we are glad to bring this simple presentation to the attention of our readers. Prepared in 1939, it aimed to present in simple terms the concepts of atomic physics and the available information about uranium. This edition provides in 7 chapters and 8 appendices much of the information on the subject that all but specialists require. The seventh appendix tells in 7 brief pages the events that led to the use of the atomic bomb against Hiroshima—a story that is officially and more fully told in Professor Smyth's report to the War Department (Princeton University Press).

The first 23 pages on the structure of the atom and atomic power possibilities will be found especially useful, also the tabular matter in the first 6 appendices. One learns of the basic work (starting with the stimulus of Einstein's theoretical equation, 1903, and extending over more than a decade) that preceded the first great practical use of atomic power. The internationalism of science is well illustrated by the various rôles played by Rutherford and the British, Hahn and Mietner, Fermi, Urey, Lawrence, Oppenheimer, and others too numerous to mention. The book is timely, and as far as one can judge about matters beyond one's field, appears to be accurate and well put together. There is an adequate bibliography, though one regrets that the index is not more detailed. E. K.

DR. W. C. ROENTGEN. By OTTO GLASSER Cleveland Clinic Foundation. Pp. 166. Springfield, Ill.: Charles C Thomas, 1945. Price, $4.50.

THE year 1945 provided the occasion for this double anniversary book, being both the centennial of Roentgen's birth and the semi-centennial of his discovery of the *X*-ray. It is based largely on the writer's biography, written in 1933, supplemented by a score of subsequent publications, letters and documents. It is a concise, clear, authoritative survey of a life of a great scientist by one who thoroughly knows his subject. *Inter alia* is included the account of Goodspeed's "accidental *X*-ray photograph" at the University of Pennsylvania in 1890, which however, was never put forward by him as a discovery but merely as "the first picture in the world (taken) by cathodic rays."

A list of Roentgen's 58 scientific papers, a chronology of his life, a Bibliography, and Index add to the usefulness of the book.

E. K.

HAHNEMANN. The Adventurous Career of a Medical Rebel. By MARTIN GUMPERT. Pp. 251. New York: L. B. Fischer, 1945. Price, $3.00.

DURING the author's 10 years in this country, he has combined the work of a busy practice with the successful completion of several entertaining books about medicine. This book, also, will be found entertaining and interesting, not only because of a lively, humorous and challenging style but also because it deals with a remarkable person. However, the author's attitude toward homeopathy, especially as expressed in the 4 pages of the "Prologue" indicates, to the Reviewer at least, that he misinterprets the rôle that homeopathy plays and has played or else that entertainment comes first in his desiderata. The Reviewer realizes that he has thus exposed himself to the same sort of criticism that is so vividly and sharply expressed in the Prologue, though he too would criticize the attitude of "the celebrated professor of internal medicine" therein portrayed. Also, the Reviewer recognizes, as he has expressed elsewhere, that homeopathy was helpful earlier in correcting therapeutic abuses and that some current practices have a superficial similarity to *similia similibus*. Nevertheless, he is far from agreeing that "a number of the most important, and newly discovered, methods of treatment . . . had been anticipated in the works of Hahnemann," he knows of no homeopathic universities in North America, and even the homeopathic medical schools have been so forced by circumstances to change their curriculum and practices that their differences from regular schools now are negligible and soon will be non-existent. In this country at least, there is no danger that in this field strife will "forever overwhelm friend and foe," because homeopathy, having made its contribution to the great stream of medical progress, is on its way out as a separate discipline. This, however, need not spoil for the reader a good story well told.

E. K.

MICROBES OF MERIT. By OTTO RAHN, Professor of Bacteriology, Cornell University. Pp. 277. Lancaster: Jacques Cattell, 1945. Price, $4.00.

IN his foreword, the author states that an enthusiastic picture of bacteria other than pathogens is needed, especially for the layman, who generally thinks all bacteria are harmful. He goes about this by giving a brief but interesting historical account of bacteriology. The main part of the book is devoted to a discussion of what microbes are and how valuable they are to man. He presents a wealth of information in an interesting manner, including the useful rôle of microbes in the production of sauerkraut, vinegar, beer and wine, alcohol, buttermilk, cottage cheese, and antibiotics such as penicillin and streptothricin. The illustrations include several humorous but purposeful cartoons. The last chapter is an epilogue in which the author suggests that a world without microbes would not be very pleasant. The book is divided into 22 chapters as follows: 1. The Smallest Beings on Earth. 2. The Discovery of Bacteria. 3. Amazing Appetites. 4. The Relatives of Bacteria. 5. Bacteria Divide When They Multiply. 6. Bacteria Can Be Tough. 7. Contamination. 8. Bacteria Among Themselves. 9. From Dust to Dust. 10. Bacteria Help the City People. 11. Bacteria Help the Farmer. 12. The 1941 Census of Bacteria. 13. Domesticated Yeasts. 14. When Bacteria Blunder. 15. Microbes and Our Daily Bread. 16. Compromise Between Man and Microbe. 17. Microbes the Food of the Future. 18. Man a Parasite of Bacteria. 19. Industry Harnesses Bacteria. 20. Inheritance Among the Sexless. 21. Bacteria Replace Guinea Pigs. 22. The World Without Microbes.

E. L.

PEDIATRIC X-RAY DIAGNOSIS. A Textbook for Students and Practitioners of Pediatrics, Surgery and Radiology. By JOHN CAFFEY, A.B., M.D., Associate Professor of Pediatrics, College of Physicians and Surgeons, Associate Pediatrician and Roentgenologist, Babies Hospital and Vanderbilt Clinic, New York City; etc. Pp. 838. Chicago: The Year Book Publishers, 1945. Price, $12.50.

ANY one who has had occasion to look for authoritative guidance on some puzzling or questionably abnormal feature of a child's roentgenogram knows that (if he has been genuinely in earnest) the search for references begins with a patient survey of the Index Medicus, and ends with a resigned acceptance of the fact that the articles on the particular subject are scattered through a diversity of unrelated periodicals, of which

only a minority of those desired are to be found in any one hospital library. It is 35 years since publication of the last book in English on pediatric roentgen diagnosis.

For this reason, and also because of its excellence and completeness, this new text book by Caffey is to be greeted warmly and enthusiastically. Here, unified under one cover, is a great body of essential information, representing the experience, studies and interpretive analysis of one of the world's experts in this expansive field. The book is simply written, remarkably well-organized, and liberally illustrated with half-tone reproductions, linear tracings, and schematic teaching diagrams. A small list of amplifying references closes each discussion. The descriptions of growth phenomena are especially fine. Every pediatrician, radiologist, surgeon and practitioner who has to cope with diagnostic problems related to childhood should have this book for handy reference. I. W.

WHAT PEOPLE ARE. A Study of Normal Young Men. By CLARK W. HEATH. Pp. 141. Cambridge: Harvard University Press, 1945. Price, $2.00.

THE reader who takes this title at face value will be disappointed. If he is wise enough to read the excellent preface by Arlie Bock, he will realize that the aim is not to tell us what people are, but to outline a program of study of this complex matter in order to indicate the approach that is being made to questions of great practical importance to which the answers must await the maturity of the boys who are studied. Present conclusions are necessarily tentative. The work is based upon the correlation of diverse techniques to achieve a comprehensive survey of each individual. These include a social study of family background, psychologic, psychiatric, physiologic, and anthropologic analyses. We await the sequel with interest. G. McC.

MEDICAL CLINICS OF NORTH AMERICA. Philadelphia Number. Symposium on Gynecology and Obstetrics. Phila: W. B. Saunders, 1945. Price, $16.00 a year.

THIS volume is a symposium on recent advances in gynecology and obstetrics, prepared principally by the staffs of the Philadelphia Lying-in Hospital and Medical College Hospital. It contains 20 reports upon a wide variety of topics. It includes among its topics of current interest: (1) some recent laboratory procedures of current interest; (2) the management of the syphilitic pregnant woman with special reference to the use of penicillin; (3) a discussion of single dose and continuing spinal anesthesia for labor and vaginal delivery; (4) the timing of ovulation by basal temperature graphs. This volume would seem to have special value for the physician just returning from the armed forces and for anyone in general practice. D. M.

THE BACTERIAL CELL IN ITS RELATION TO PROBLEMS OF VIRULENCE, IMMUNITY, AND CHEMOTHERAPY. By RENE J. DUBOS, George Fabyan Professor of Comparative Pathology and Professor of Tropical Medicine and Public Health, Harvard University, and member of the Rockefeller Institute. With an Addendum by C. F. ROBINOW, Strangeways Laboratory, Cambridge, Eng. Pp. 460; 33 ills. Cambridge, Mass.: Harvard University Press, 1945. Price, $6.00.

BY reviewing much of the recent literature on bacterial anatomy and physiology, the author presents a correlation, as far as existing data permit, of ideas and facts concerning bacterial make-up and function. Knowledge about bacterial structure is gained directly from study of stained preparations, dark-field microcinematography, and electron micrography. Chemical and serologic studies have yielded information concerning cellular components. In some instances such procedures indicate actual morphologic positions of these products such as capsular antigens or somatic surface antigens. A study of bacterial enzyme systems leads to knowledge of microbial function. The known relationships between bacterial variability and enzyme activity variation are considered. The author minutely discusses the use of the term, "virulence," in relation to pathogenic bacteria and their hosts. The problem of bacterial dissociation applied to immunization procedures, or the use of isolated bacterial antigens for the same purpose in man and animals, entails not only a discussion of the development of type specific immunity but also a consideration of the relatively little studied group specific or broadly specific

immunity. The probable mechanisms of action of bacteriostatic agents, particularly the sulfonamides, are developed here in moderate detail. Such discussions of the chemotherapeutic agents fit into the theme of the book through their ability to inhibit bacterial function and enzymes, or to cause dissociation. In attempting to correlate the observations of many investigators on bacterial structure and properties the author incorporates the opinions of those whose work he cites as well as his own. The Addendum by C. F. Robinow presents detailed considerations of bacterial structures of somewhat controversial nature, such as the problem of the bacterial nucleus. Throughout the book, evidence from the literature in support of statements is presented in the form of numerous charts, figures, and photographs. The bibliography is extensive and broad in scope. This book can be recommended particularly for those persons working in the fields of bacteriology or investigative preventive medicine as well as for students entering the fields. J. F.

TEXTBOOK OF MEDICINE. Edited by J. J. CONYBEARE, M.C., D.M., Oxon., F.R.C.P., Physician of Guy's Hospital, London. Seventh Ed. Pp. 1164. Baltimore: Williams & Wilkins, 1945. Price, $8.00.

THE 1945 edition of Conybeare's Textbook of Medicine compares unfavorably with the available textbooks of medicine by American authors. The first item contributing toward this unfavorable impression was the absence of 4 pages from the Table of Contents of the reviewer's copy. A more important defect was a failure of the contributors to include recent medical advances in their discussion. In the field of chemotherapy the sulfonamides did not receive the attention they deserved; it is amazing to realize that sulfadiazine is little known in Britain and not readily available. Sulfamerazine is unmentioned and readers are referred to the literature for information on penicillin.

Many other sections were notably deficient. The diseases of the thyroid gland and liver were not brought up to date. In the cardiologic section it was surprising to find the value of precordial electrocardiography questioned, and the drug, aminophyllin, apparently unknown and unused.

One amusing item, for American readers at least, was the use of the 14 pound archaic "stone" as a unit of weight in the discussion of diabetes.

In no part of the book is the reader furnished with references for the material presented and he is left with the feeling that most of the statements are based on clinical impression rather than on controlled observations by the authors or others. In all of the presentations, there is very little correlation between pathologic and physiologic changes.

R. M.

THE CARE OF THE NEUROSURGICAL PATIENT —Before, During and After Operation. By ERNEST SACHS, A.B., M.D., Professor of Clinical Neurological Surgery, Washington University School of Medicine, St. Louis. Pp. 268; 177 ills., including 2 in color. St. Louis: C. V. Mosby Co., 1945. Price, $6.00.

THE vast experience of the dean of American neurologic surgeons has been utilized in the preparation of this monograph. The career of Dr. Sachs, extending through the entire period of modern neurosurgery, is reflected in this book; it is of great value to younger men to be informed of the various stages of growth through which neurosurgical technique has passed.

The precise details of examination, of preoperative care, of the various operative procedures, and of the postoperative problems are presented. The discussion of such points as the proper position for the patient, the diet, the care of the bowels, use of medications, dressing of wounds, etc., will be welcomed by the new resident in neurologic surgery. Features in the care of the unconscious or uncoöperative patient, seldom presented in other texts, receive adequate consideration here. A more detailed discussion of cerebral edema and measures to combat this principal postoperative difficulty, such as by ventricular puncture, should perhaps have also been included.

The more experienced neurosurgeon will appreciate the description given of Dr. Sachs' operating clinic and technique, from which many points gained through years of trial and elimination are made available for the reader's consideration. The chapter on anesthesia is not as complete as one might wish, and no longer do all neurosurgeons or anesthetists share the enthusiasm for avertin expressed in this book.

This well written and well illustrated con-

cise monograph can be heartily recommended to all interested in this subject. It will, of course, be of principal value to those just embarking on their careers in neuro-surgery.

F. G.

FUNDAMENTAL PRINCIPLES OF PHYSICAL CHEMISTRY. By CARL F. PRUTTON, PH.D., Professor of Chemistry and Chemical Engineering, and SAMUEL H. MARON, PH.D., Associate Professor of Physical Chemistry, Case School of Applied Science, Cleveland, Ohio. Pp. 780. New York: Macmillan, 1944.

THIS new book is primarily intended as a textbook for a full year course in physical chemistry for chemistry and chemical engineering students. As such it of course covers completely all aspects of the subject. Much, but not all, of the material would be applicable to a shorter course such as is often given to students in the various branches of the biological sciences. As the authors suggest, it can be adapted for such a course by judicious selection of subjects. They do not however suggest any program but leave details to the instructor.

The authors have made no radical innovations in presenting their material. Major topics covered are gases, liquids, solids, solutions, colloids, thermochemistry, electrolytic phenomena, ionic equilibrium, kinetic reactions, atomic and molecular structure and the correlation of such structure with physical and chemical properties. The text is well organized and well written. At the end of each chapter is a short useful bibliography. The printing and binding are good, indeed better than most wartime offerings. Certainly this book can be well recommended as a text for students of chemistry and allied sciences.

W. S.

WHAT TO DO ABOUT VITAMINS. By ROGER J. WILLIAMS. Pp. 56. Norman: University of Oklahoma Press, 1945. Price, $1.00.

THE discoverer of Pantothenic Acid has written a very interesting and informative book about what he has called "food lubricants," *i. e.*, the vitamins and minerals, in contrast to the "food fuels."

The volume adds to the sources available for intelligent readers who want to know more about diet and health. Aids to teaching the subjects are numerous and original.

E. W.

HEMATOLOGY FOR STUDENTS AND PRACTITIONERS. By WILLIS M. FOWLER, A.B., M.D., Professor of Internal Medicine, University of Iowa, Iowa City. With a chapter by ELMER L. DEGOWIN, A.B., M.D., Assistant Research Professor of Medicine, University of Iowa, Iowa City. Pp. 499; 8 plates, 110 figs. New York: Hoeber, 1945. Price, $8.00.

THIS is a good, practical text for students and practitioners, written by a careful, conscientious, able teacher. The essentials of clinical hematology are well presented. The color plates are excellent and most of the photomicrographs and other figures are complementary and illuminating. The chapter by Dr. Degowin on transfusion is especially up-to-date and authoritative. A few minor errors of omission and commission might be mentioned, and a "watch-dog" type of critic might raise the question of the over-all need for this latest hematologic text book. This reviewer, however, likes this book and recommends it to sophomore and senior medical students and to returning veteran medical officers and other practitioners who want a sound review of the old and an introduction to the new in clinical hematology.

T. F-H.

CLASSIC DESCRIPTIONS OF DISEASE. With Biographical Sketches of the Authors. By RALPH H. MAJOR, M.D., Professor of Medicine, University of Kansas School of Medicine. Pp. 679. Springfield: Charles C Thomas, 1945. Price, $6.50.

As our previously expressed praise (AM. J. MED. SCI., June, 1933 and April, 1939) of this valuable book remains unchanged, we content ourselves with noting the following major (no pun intended!) additions: Hodges, N., *Loimologia;* Nott, J., *Yellow Fever Contrasted With Bilious Fever;* Home, F., *An Enquiry Into the Nature, Cause and Cure of the Angina Suffocativa,* etc.; Cober, T., *The Hungarian Disease;* Louis, Pierre, *The Disease Known Under the Names of Gastro-enteritis, Putrid, Adynamic, Ataxic, Typhoid Fever,* etc.; Vieusseux, G., *Cerebral Malignant Non-contagious Fever;* North, E., *Malignant Epidemic Commonly Called Spotted Fever;* Hippocrates, *Mumps;* DaCosta, J., *On Irritable Heart;* Riverius, L., *Caruncles Resembling a Cluster of Hazelnuts;* Battista, G., *Excrescences on the Valves;* Bouillaud, J.,

Confluent Vegetations on the Valves; Virchow, R., *Concerning Acute Inflammation of the Arteries;* Kirkes, W., *Detachment of Fibrinous Deposits From the Interior of the Heart;* Winge, E., *Mycosis endocardii;* Vitry, J., *A Certain Pestilence;* Sire de Joinville, J., *The Army Sickness;* Aretaeus, *On the Coeliac Affection;* Heberden, W., *Of the Nyctalopia or Night-Blindness;* Graves, R., *Fugitive Inflammation.*

There is a welcome addition of an 11-page bibliography which gives from 1 to 13 references each, on 179 celebrities. The thinner paper used—perhaps unavoidably—gives a smaller, lighter volume, to be sure, but also a sheet that is less easily read and more prone to wrinkle. E. K.

NEW BOOKS

Manual of Diagnosis and Management of Peripheral Nerve Injuries. By ROBERT A. GROFF, M.D., LT. COL., M.C., A. U. S., formerly Assistant Professor of Surgery, Jefferson Medical College, and Assistant Professor of Neurosurgery, Graduate School of Medicine, University of Pennsylvania, and SARA JANE HOUTZ, B.S., 1ST LIEUT. (P.T.) A. U. S. With an Introduction by I. S. RAVDIN, M.D., BRIG. GENERAL, M.C., A. U. S., John Rhea Barton Professor of Surgery, University of Pennsylvania. Pp. 188; 111 ills. Phila.: Lippincott, 1945. Price, $8.00.

An Introduction to Physical Anthropology. By M. F. ASHLEY MONTAGU, Associate Professor of Anatomy, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania, Visiting Lecturer, Department of Sociology, Harvard University. Pp. 325. Springfield, Ill.: Thomas, 1945. Price, $4.00.

A Future for Preventive Medicine. By EDWARD J. STIEGLITZ, M.S., M.D., F.A.C.P. Pp. 73. New York: The Commonwealth Fund, 1945. Price, $1.00.

The Psychoanalytic Theory of Neurosis. By OTTO FENICHEL, M.D. Pp. 703. New York: W. W. Norton & Company, Inc., 1945. Price, $7.50.

War Neuroses. By ROY R. GRINKER, LT. COL., M.C., and JOHN P. SPIEGEL, MAJOR, M.C., Army Air Forces. Pp. 145. Phila.: The Blakiston Co., 1945. Price, $2.75.

Everybody's Way to Health and Fitness. By T. R. TOGNA. The Influence of Exercises in the Bath on the Circulatory and Respiratory Systems. With Introductions by SIR LEONARD HILL, M.B., F.R.S., LL.D., formerly Director, Department of Allied Physiology and Hygiene, National Institute of Medical Research, London, and DR. JENNER HOSKIN, M.D., F.R.C.P. London: The Caxton Press, Ltd., 1945. Price, 5s.

Sir Leonard Hill says in his Introduction, "The attention of physio-therapeutists might well be directed to Mr. Togna's work. . . . He has proved the great value of such exercises, and were they widely practised a great deal of rheumatic pain and disability together with cardio-vascular disease in old age might be prevented."

Advances in Protein Chemistry. Volume II. Edited by M. L. ANSON, Continental Foods, Hoboken, and JOHN T. EDSALL, Harvard Medical School, Boston. Pp. 443. New York: Academic Press, 1945. Price, $6.50.

Pathology in Surgery. By N. CHANDLER FOOT, M.D., Professor of Surgical Pathology, Cornell University Medical College, Surgical Pathologist, New York Hospital. Pp. 511; 368 ills. Phila.: Lippincott, 1945. Price, $10.00.

Advances in Carbohydrate Chemistry. Volume I. Edited by W. W. PIGMAN, Corn Products Refining Co., Argo, Ill., and M. L. WOLFROM, The Ohio State University, Columbus, Ohio. Pp. 374. New York: Academic Press, 1945. Price, $6.00.

Men Without Guns. Text by DEWITT MACKENZIE, War Analyst of The Associated Press. Descriptive Captions by MAJOR CLARENCE WORDEN, Medical Department of the United States Army. Foreword by MAJOR GENERAL NORMAN T. KIRK, Surgeon General of the United States Army. Pp. 152; 137 ill. Phila.: Blakiston, 1945. Price, $5.00.

Clinical Roentgenology of the Heart. (Annals of Roentgenology) Volume XVIII. By JOHN B. SCHWEDEL, M.D., Asso. Attending Physician, Medical Division, Adjunct Attending Physician, Dept. of Roentgenology, Montefiore Hospital, New York, etc. Pp. 380; 749 ills. New York: Paul B. Hoeber, 1945. Price, $12.00.

NEW EDITIONS

American Red Cross First Aid Textbook. Prepared by the American Red Cross for the Instruction of First Aid Classes. Revised with 264 ills. Pp. 254. Phila.: Blakiston, 1945.

This edition of the well-known textbook for "first-aiders" has had the advantage of the close coöperation and supervision of experts of the Division of Medical Sciences of the National Research Council and of profiting by the experiences—military and civilian—of World War II. The results appear in many of the pages and illustrations. It is a much more practical as well as up-to-date book than the 1937 edition ever was.

E. K.

NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

MANUSCRIPTS intended for publication in THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. EDWARD B. KRUMBHAAR, School of Medicine, University of Pennsylvania, Philadelphia 4, Pa. Articles are accepted for publication in THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively, except in the case of subsequent publication in Society proceedings.

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